THE SYNTHETIC AND BIOLOGICAL STUDY OF BRYOSTATIN ANALOGUES

by

Wei Li

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STATEMENT OF DISSERTATION APPROVAL

The dissertation of **Wei Li**

has been approved by the following supervisory committee members:

Gary E. Keck	, Chair	**01/19/2011** Date Approved
Matthew S. Sigman	, Member	**01/19/2011** Date Approved
Janis Louie	, Member	**01/19/2011** Date Approved
Richard D. Ernst	, Member	**01/19/2011** Date Approved
Chris M. Ireland	, Member	**01/19/2011** Date Approved

and by **Henry S. White** , Chair of the Department of **Chemistry**

and by Charles A. Wight, Dean of The Graduate School.

ABSTRACT

Bryostatins is a novel family of marine natural products that were originally isolated by Pettit from the bryozoan *Bugula neritina*. Since its isolation, bryostatin 1 has gained extensive attention due to its unique biological activities. It has been shown to restore the apoptosis of cancer cells, reverse the multidrug resistance, stimulate the immune, synergize with other antineoplastic agents. Bryostatin 1 also demonstrates its capabilities of promotion of memory, recovery from the stroke and treatment of Alzheimer's Disease. All those unique bioactivity are possibly related to the interaction with protein kinase C isozymes (PKC). Bryostatin 1 has been proved to be able to activate PKC through the binding with C1 domain of PKC, which initiates a variety of downregulation responses to the proliferation, division and apoptosis of cell. Bryostatin 1 is not the only ligand binding with PKC C1 domain. In comparison with other PKC activator such as phorbol esters, bryostatin 1 is nontumor promoting, can even antagonize the tumor promoting effect of phorbol ester, which makes it in the front line for the development of new drug lead that target PKC.

The research on bryostatin has been hampered by its limited supply due to the low abundance in nature source. Our group has been involved in the synthesis of bryostatin and analogues to solve the problem of supply of bryostatin. Described herein is the exploration of convergent and efficient routes to prepare bryostatin analogues. Pyran annulation has been proven to be versatile and tolerant of functional groups in

construction of 2,6-*syn* pyran. Its application in our analogue synthesis successfully delivered the target molecules, which demonstrated high binding affinity with PKC, but the biological result of bryostatin analogue with C7 acetate indicated it behaved like phorbol ester instead of bryostatin 1.

In order to understand the role of northern hemisphere of bryostatin on its biological activities, analogue with functional group on different positions in the northern region is investigated systematically. The biological results from these analogues will help us to clarify the pharmacophoric groups that define the unique biological activities of bryostatin 1.

Dedicated to my family for their endless love and support

TABLE OF CONTENTS

STANDARD LIST OF ABBREVIATIONS

$[\alpha]_D^{20}$	specific rotation
Ac	acetyl
AcOH	acetic acid
$AlMe_3$	trimethyl aluminum
BBr_3	boron tribromide
BF_3•OEt_2	boron trifluoride diethyletherate
BH_3•THF	borane tetrahydrofuran complex
BINOL	(1,1-binapthalene)-2,2-diol
BITIP	catalyst made by combining (1,1-binapthalene)-2,2-diol and Ti(O*i*-Pr)$_4$
Bn	benzyl
$B(OMe)_3$	trimethylborate
BPS	*tert*-butyldiphenylsilyl
n-Bu	butyl
t-Bu	*tert*-butyl
n-BuLi	*n*-butyllithium
Bu_3B	tributylborane
Bu_2BOMe	methoxy dibutylborane
Bu_2BOTf	dibutylboron triflate
Bz	benzoyl

°C	degrees Celsius
CAA	catalytic asymmetric allylation
calcd	calculated
$CDCl_3$	deuterated chloroform
CDI	carbonyldiimidazole
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane
C1	cysteine rich domain
COSY	correlation spectroscopy
CSA	10-camphorsulfonic acid
d	day(s); doublet (spectral)
DCC	1,3-dicyclohexylcarbodiimide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene,
DDQ	2,3-dicyano-5,6-dichloro-parabenzoquinone
de	diastereomeric excess
dr	diastereomeric ratio
DEPT	distortionless enhancement by polarization transfer
DIBALH	diisobutylaluminun hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMAP•HCl	4-dimethylaminopyridinium hydrochloride
DMPU	N,N'-dimethyl-N,N'-propylene urea
DMF	dimethylformamide
DMP	dimethoxypropane
DMS	dimethylsulfide

DMSO	dimethyl sulfoxide
DQCOSY	double quantum correlation spectroscopy
EDCI	1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide
EI	electron ionization
er	enantiomeric ratio
equiv	equivalent(s)
Et	ethyl
EtOH	ethanol
Et_2O	diethylether
EtOAc	ethyl acetate
EI	electron impact
ESI	Electrospray ionization
FAB	fast atom bombardment
g	gram(s)
h	hour(s)
HF•py	hydrogen fluoride pyridine complex
HMDS	hexamethyldisilazane
HRMS	high-resolution mass spectrum
Hz	hertz
IC_{50}	50% inhibitory concentration
IR	infrared
J	coupling constant (in NMR)
K_i	binding affinity
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide

LiHMDS	lithium hexamethyldisilazide
LRMS	low-resolution mass spectrum
L-Selectride®	lithium tri-*sec*-butylborohydride
M	molarity, mol/L; mega
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeLi	methyl lithium
MeOH	methanol
MHz	megahertz
min	minute(s)
mL	milliliter
MMPP	magnesium monoperoxyphthalate
MNBA	2-methyl-6-nitrobenzoic anhydride
mol	mole(s)
mp	melting point
MS	mass spectrometry; molecular sieves
Ms	methanesulfonyl
MTPA	α-methoxy-α-trifluoromethylphenylacetate
M/Z	mass to charge ratio (in mass spectrometry)
NaH	sodium hydride
NaHMDS	sodium hexamethyldisilazide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance

NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
PCC	pyridinium chlorochromate
Ph	phenyl
PKC	protein kinase C
PMB	*para*-methoxybenzyl
$P(OEt)_3$	triethylphosphite
ppm	parts per million (in NMR)
PPTs	pyridinium *p*-toluenesulfonate
*i*Pr	isopropyl
$(iPr)_2NH$	diisopropylamine
py	pyridine
q	quartet (spectral)
quant	quantitative
R_f	retention factor (in chromatography)
RCM	Ring-Closing Metathesis
rt	room temperature
s	singlet (spectral); second(s)
sp.	species
SO_3•py	sulfur trioxide pyridine complex
t	triplet (spectral)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxyl
TES	triethylsilyl

Tf	trifluoromethanesulfonyl, triflate
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl, tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TNFα	tumor necrosis factor alpha
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl, tosic
TsOH	*p*-toluenesulfonic acid

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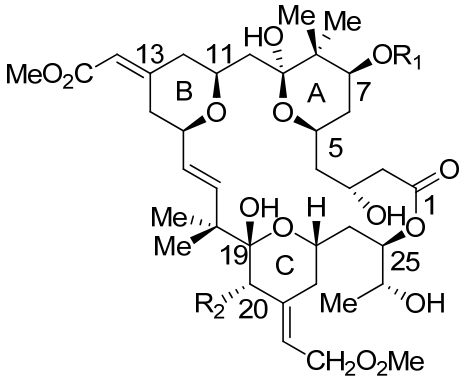
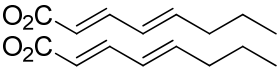
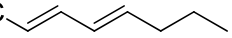
CHAPTER 1

INTRODUCTION OF CHEMISTRY AND BIOLOGY OF BRYOSTATINS

Introduction

The bryostatins are a novel family of marine natural products with exceptional bioactivities. During the 1960s, Pettit and coworkers found that extracts from the marine bryozoan *Bugula neritina* from the Gulf of Mexico demonstrated antitumor effects.[1] The active components were not identified until 1982 when the Pettit group isolated and characterized bryostatin 1 with the help of crystallographic and spectroscopic techniques.[2] The absolute stereochemistry of bryostatin 1 was confirmed by the same group in 1991 using X-ray crystallography of the heavy atom containing C7 para-bromobenzoate derivative of bryostatin 2.[3] Since then more bryostatins were added into the family which currently consists of a total of 20 members.[4-13] The structures of bryostatins 1-20 are summarized in Figure 1.1. Each member of the bryostatin family is characterized by a 20-membered macrolactone in which there are three embedded highly substituted pyran rings linked by a C16-C17 (*E*)-disubstituted olefin and a methylene bridge; all family members also contain a pair of geminal dimethyls at C8 and C18, as well as an exocyclic methyl enoate in their B and C rings. Besides their structural differences of the substituents on C7 and C20, bryostatins 3 19, and 20 have a butenolide appended to the C-ring, bryostatins 15-17 have a simplified C ring of glycal, and bryostatins 17 and 18 have opposite methyl enoate geometry in the C ring.



Bryostatin 1: R_1=Ac, R_2= 
Bryostatin 2: R_1=H, R_2=
Bryostatin 4: R_1=CO-*i*-Bu, R_2=OCO-*n*-Pr
Bryostatin 5: R_1=CO-*i*-Bu, R_2=OAc
Bryostatin 6: R_1=CO-*n*-Pr, R_2=OAc
Bryostatin 7: R_1=Ac, R_2=OAc
Bryostatin 8: R_1=CO-*n*-Pr, R_2=OCO-*n*-Pr
Bryostatin 9: R_1=CO-*n*-Pr, R_2=OAc
Bryostatin 10: R_1=CO-*t*-Bu, R_2=H
Bryostatin 11: R_1=Ac, R_2=H
Bryostatin 12: R_1=CO-*n*-Pr, R_2= 
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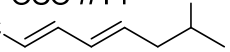
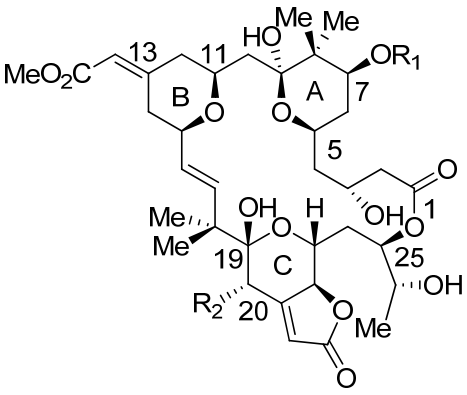
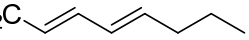
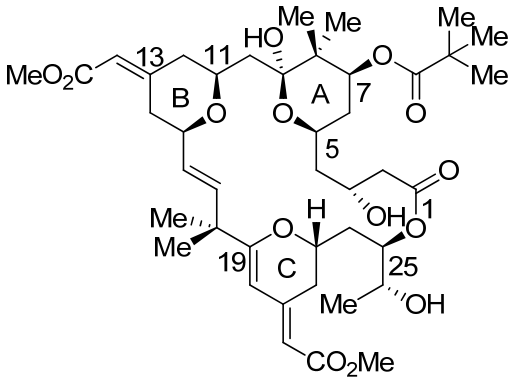
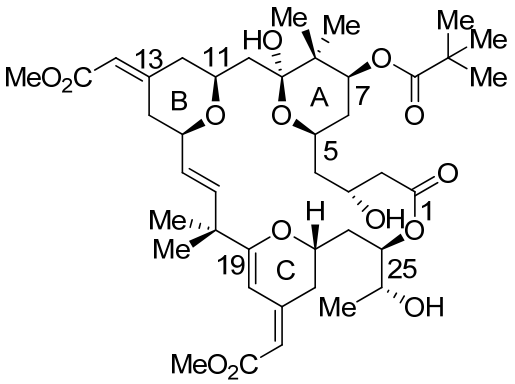
Bryostatin 15: R_1=Ac, R_2= 



Bryostatin 3: R_1=Ac, R_2= 
Bryostatin 19: R_1=CO-*t*-Bu, R_2=OCO-n-Pr
Bryostatin 20: R_1=CO-*t*-Bu, R_2=H



Bryostatin 16



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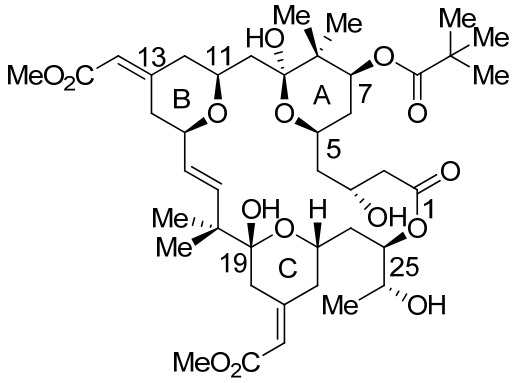


Bryostatin 18

Figure 1.1 Structures of bryostatins

The bryozoans do not intend to produce bryostatins as an anti-cancer drug candidate, but as a chemical defender against predators. The Lopanik group found that bryostatins isolated from the larvae of bryozoan significantly reduced their palatability to the pinfish,[14] making it extremely likely that bryostatins play a role in the chemical defense of these young animals.

Biosynthetic studies suggest that complex polyketides such as the bryostatins are synthesized by modular polyketide synthases (PKS).[15] Modular PKS are typically only found in bacteria, which makes the bacterial symbiont of B. *neritina* a prime candidate for the true biosynthetic source of the bryostatins. The bryozoan harbors an uncultivated gamma proteobacterium, "*Candidatus* Endobugula *sertula*," which is passed to the larvae prior to their release from the adult. The confirmation of *E. sertula* as the true source of bryostatin has proved to be a difficult challenge due to the inability to cultivate these symbiotic bacteria. The Haygood group successfully cloned and sequenced the genes in the uncultivated *E. sertula*, among which there is a type I polyketide synthase (PKS-I).[16] The required β-ketoacyl synthase (KS) domain, for each elongation and modification step in the synthesis of the polyketide chain, was also found in the symbiont. Inhibition of *E. sertula* with the antibiotic gentamicin sulfate resulted in reduced detection of PKS-I and KS genes, as well as the reduction of bryostatin synthesis.[16] Interestingly, this reduction, however, was not proportional to the loss of bacterial symbiont (46% loss in bryostatin activity compared to 95% estimated loss of "*E. sertula*"), which suggests the biosynthesis of bryostatins is more complicated than originally thought, and it may be under the control of the symbiont or the host and may be up-regulated when bacterial numbers are reduced.

The bryostatin gene clusters identified by the Haygood group consist of two groups: five genes (bryA-D and X) totaling 71 kb coding for modular PKSs and four genes (bryP-S) totaling 6 kb with accessory functions.[17,18] Based on their discovery, the Haygood group proposed a biosynthetic pathway for bryostatins (Figure 1.2). The hypothetical biosynthesis starts with lactate, from which the four PKS genes bryA-D will elongate the carbon chain to C27. The common intermediate to all bryostatins is proposed as bryostatin 0 after manipulation from genes bryD, or bryo X, bryR and bryS. The further modification of bryostatin 0 would lead to all of the bryostatins.

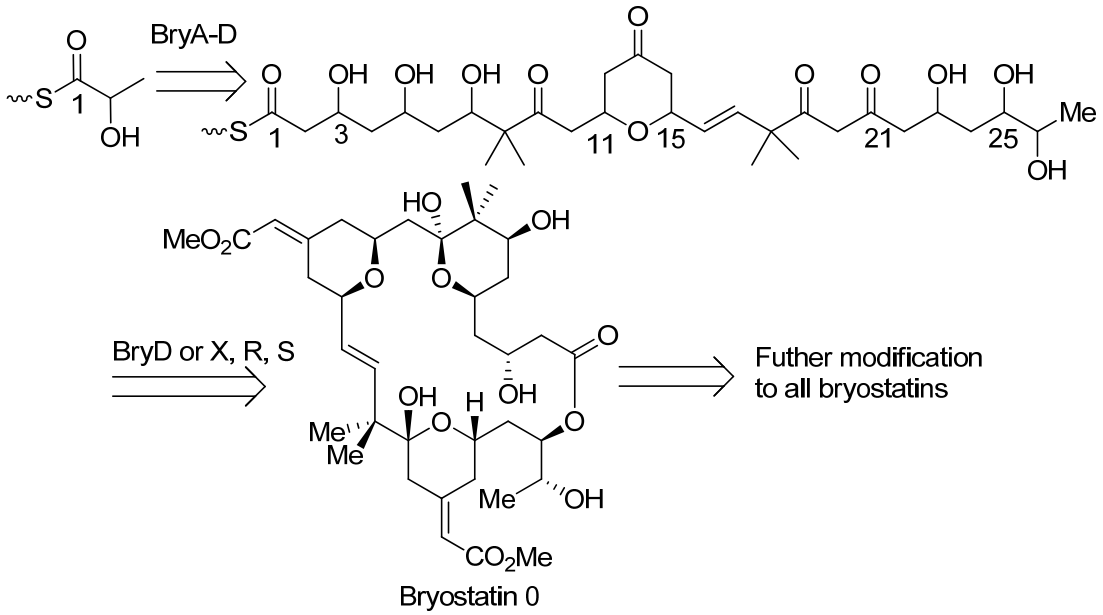


Figure 1.2 Proposed biosynthetic pathway to bryostatins

Biological Activities of Bryostatins

Since their discovery, bryostatins have received tremendous attention from the community of biologists and chemists due to their unique bioactivities. Initially, bryostatins were investigated due to their remarkable in vitro and in vivo anti-tumor effects against a range of cancer cells including HL-60 Human promyelocytic leukemia cells,[19] P388 lymphocytic leukaemia,[2] B16 melanoma,[20] and M5076 reticulum cell sarcoma.[21] These promising results led to the clinical trials of bryostatin 1 against a variety of cancers.[22-25] Bryostatin 1 alone or in combination with other chemotherapeutic drugs has been involved in over 80 clinical trials.[26] Although clinical results indicate that bryostatin 1 alone shows limited potential, its use in combination with existing chemotherapies has shown great promise. When bryostatin 1 is coadministrated with other anti-cancer drugs such as paclitaxel,[27] vincristine,[28] cisplatin,[29] fludarabine,[30] etc., a synergetic effect, the reversion of multidrug resistance,[31] and protection of cells from ionizing radiation and restoration of apoptotic function are observed.[32]

The anti-tumor effects of bryostatin 1 are generally believed to be due to its ability to selectively modulate the function of various individual protein kinase C (PKC) isozymes within the cell.[33] PKC is a class of serine/threonine isozymes catalyzing the O-phosphorylation of a variety of protein targets and transducing a myriad of signals, which are essential for celluar functions such as cell division, proliferation, differentiation and apoptosis.[34-36]

The PKC family comprises 10 isozymes grouped into 3 classes: conventional or classic (PKC α, βI, βII and γ), novel (PKC δ, ε, η and θ), and atypical (PKC ζ and ι).[37] All family members share the same architecture: a carboxyl terminal kinase domain linked by

a flexible hinge segment to an amino-terminal region containing regulatory modules (Figure 1.3). This regulatory moiety contains two key functionalities: an autoinhibitory sequence and one or two membrane-targeting modules (C1 and C2 domains). The regulatory moiety of conventional PKC is composed of two tandem C1 domains, allowing them to respond to ligand binding such as second messenger diacylglycerol (DAG), and a C2 domain, which binds a Ca^{2+} ion. Novel PKC also contain two tandem C1 domains, conferring DAG sensitivity, but they contain a "novel" C2 domain that does not bind Ca^{2+} and does not serve as a membrane-binding module. Atypical PKC possess an "atypical" highly basic C1 domain which prevents ligand binding, so these isozymes respond to neither DAG nor Ca^{2+}. The activation of different classes of PKCs requires different activators due to the structural difference. The activity of conventional PKC isozymes is stimulated by DAG, Ca^{2+}, and phosphatidylserine, that of novel isozymes by DAG and phosphatidylserine, and that of atypical PKC's by phosphatidylserine only.

PKC plays a key role in intracellular signal transduction. A wide range of external signals, including hormones, neurotransmitters, growth factors and cytokines, promote the stimulation of the isoforms of the phospholipase C (PLC1) family. PLCs catalyze the hydrolysis of phosphatidylinositol 4,5-bisphosphate to produce two secondary messengers: inositol-1,4,5 triphosphilate (IP_3), which triggers the release of Ca^{2+} from internal stores; and DAG, which initiates cellular responses through a variety of effectors. The most prominent intracellular targets of DAG are the PKC isozymes.

When PKC is inactive, the pseudosubstrate lying N-terminal to the C1 domain occupies the substrate-binding cavity of PKC. In this closed, autoinhibited conformation, PKC is relatively resistant to proteolysis. The activation of PKC requires three properly

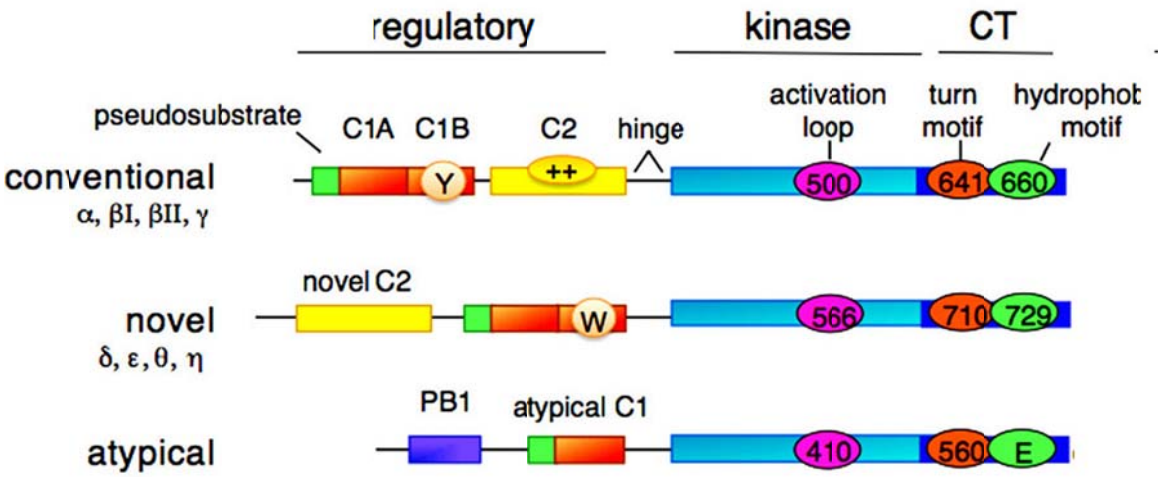


Figure 1.3 Structure of protein kinase C[36]

ordered phosphorylations: activation loop phosphorylation, turn motif phosphorylation, and hydrophobic motif phosphorylation.[38] After the phosphorylation, in the case of conventional PKCs, the engagement of DAG with the C1 domain and Ca^{2+} with the C2 domain will translocate PKC to the cellular and nuclear membrane, which also provides the energy to release the autoinhibitory pseudosubstrate to initiate downstream signaling events. The activated catalytic domain then binds and phosphorylates specific substrates. The translocation of PKC onto the membrane is the hallmark of activation of PKC. Novel PKCs without a Ca^{2+}-binding C2 domain have a C1 domain that binds diacylglycerol-containing membranes with an order of magnitude higher affinity than the C1 domain of conventional PKCs. The activation of atypical PKCs responding to neither DAG nor calcium is regulated by phosphorylation by 3-phosphoinositide dependent protein kinase-1(PDK1).

The activation and maturation of PKC is only the first step during its performance in signal transduction. When PKC associates with membrane, it is dephosphorylated by

membrance-bound alkaline phosphatases, which converts it into a catalytically inactive form. The inactive PKC is then degraded following ubiquitination downregulation in the process known as.[38]

DAG is not the only ligand capable of binding with C1 domains and activating PKC, in fact there are a variety of structurally different compounds proven to bind with the same C1 domain in PKC (Figure 1.4). Phorbol esters are a group of 11 tetracyclic diterpene natural products isolated from the croton oil.[39] They were found to be the potent tumor promoting substances. Among them, phorbol 12-myristate 13-acetate (PMA) is the most potent one.

The phorbol esters initially became the object of intense research interest on the basis of their potent activity as mouse skin tumor promoters.[40] The identification of PKC as the major target for the phorbol esters suggests that the phorbol esters can be very

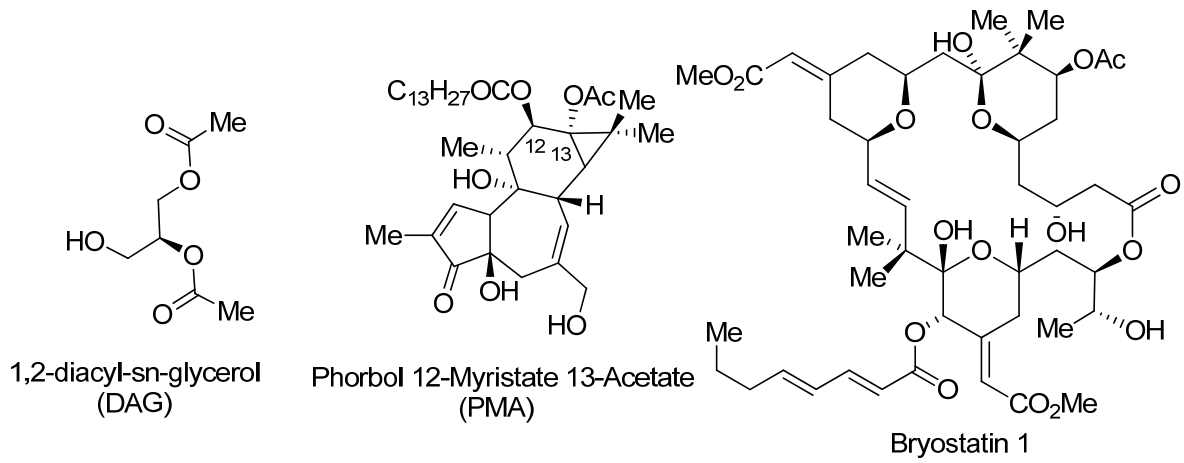


Figure 1.4 Structures of protein kinase C activators

useful probes for identifying the physiological systems in which PKC is involved. Finally, the detailed understanding of the interaction of phorbol esters with the regulatory domain on PKC might permit the development of agents which interfere with protein kinase C activity, thereby functioning as anti-promoters or as inhibitors of physiological effectors.

The Zhang group was able to acquire the X-ray structure of the PKCδ C1 domain complex with PMA.[41] The X-ray structure shows phorbol ester binding does not produce a significant conformational change within the activator-binding domain. Rather, it inserts into the groove and replaces the water molecules inside. PMA acts to cover the polar interior of the groove and completes a contiguous hydrophobic surface over a large portion of the C1 domain. The long-chain lipid tails of PMA are probably not directly involved in binding to PKC, but instead retain the activator within the membrane.

Bryostatin 1, like phorbol ester, has been shown to be a potent activator of PKC through the binding with the C1 domain. However, despite sharing the same binding sites, bryostatin 1 has antineoplastic properties that, in fact, can inhibit phorbol ester-mediated tumor promotion.[42] This disparity is not completely understood but is attributed to differences in the down regulation of PKC. Studies from the Blumberg group indicated bryostatin 1 and PMA showed different down-regulation of PKCδ in different cell lines. Bryostatin 1 can initiate a biphasic pattern of down-regulation of PKCδ, with reduced down-regulation at higher bryostatin 1 concentrations, whereas PMA causes monophasic down-regulation. This pattern of behavior has been seen in U937 cells,[43] NIH3T3 cells,[44] primary mouse keratinocytes,[45] B16/F10 melanocytes,[46] and HOP-92 cells.[47] Bryostatin 1 at high concentrations (100–1000 nM) blocks the response induced by PMA through differentially modulating PKCδ translocation and preventing PKCδ-mediated release of

tumor necrosis factor-α (TNF-α). These results suggest byrostatin 1 anticancer activity in some cells to be attributable to protection and stabilization of PKCδ from PMA.

It is important to emphasize that the extracellular signal transduction is extremely complex. PKC isozymes are not the sole family of proteins with C1 domains that recognize DAG, phorbol esters and bryostatin 1. Other C1 domain-containing proteins, such as PKD, DGKs, RasGRPs, chimaerins, Munc13s, and MRCKs, might also be the targets of bryostatin 1. The actual mode of action of bryostatin 1 is still controversial and an important area of research.

Additionally, bryostatin 1 has been found to have immunostimulant effects,[48-51] as well as promoting the synthesis of protein necessary for long term memory,[52,53] and aiding recovery from stroke.[54] Even more interestingly, bryostatin 1 is indicated as a potential therapeutic candidate for the treatment of Alzheimer's disease (AD).[55,56] The FDA recently has approved a clinical trial of bryostatin 1 directed by the Alkon group for the treatment of AD.[57]

Alzheimer's disease is the most common form of dementia, a general term for loss of memory and other intellectual abilities serious enough to interfere with daily life. In 2006, the worldwide prevalence of Alzheimer's disease was 26.6 million. By 2050, the prevalence is expected to quadruple, by which time 1 in 85 persons worldwide will be living with the disease.[58] The underlying cause of AD is still not fully understood, however amyloid beta (Aβ) deposits are believed to be associated with the cause of this disease. The processing of amyloid protein precursor (APP) and its metabolic products plays a fundamental role in AD pathophysiology. APP is a large transmembrane protein that can be cleaved in three distinct sites by proteolytic enzymes collectively referred to

as ‘‘secretases’’, among which α-secretase cleaves within the Aβ sequence to generate a large extracellular soluble fragment (sAPP α). These fragments appear to have no pathological significance and sAPP α might even have neuroprotective properties. A deficiency of PKC activation could increase levels of amyloid β, resulting in amyloid plaques. The deficiency of PKC activation also could increase levels of phosphorylated tau (owing to reduced PKC-mediated inhibition of GSK-3b) and resulting neurofibrillary tangles. Bryostatin 1 markedly enhances the α-processing of APP by enhancing secretion of the α-secretase product sAPP α, resulting in reduced formation of amyloid plaques. Most recently, the Alkon group found that significant cognitive deficits occurred on mice five months before plaques were detected in their brains, providing evidence that plaques and tangles are not at the root of the disease.[59] They also found the treatment of bryostatin could control the creation of synapsis and restore the space learning and memory of mice. Given its lack of tumor promotion activity, relatively low toxicity, and current use in clinical trials for cancer treatment, bryostatin 1 offers a plausible approach for developing AD therapeutics.

While the remarkable biological activity of bryostatins has generated great attention for its potential uses as a therapeutic agent, the limited natural availability of those compounds has hindered the research on bryostatins. The isolation yield of bryostatins varies from 10^{-5}% to 10^{-3}% dependent on the location of bryozoan. The largest isolation of bryostatins provided 18 g of compounds from 13,000 kg of wet animals.[60] An attempt by CalBioMarine Technologies to aquaculture Bugula neritina failed to produce a substantial supply. Currently, the only viable method to prepare bryostatins and their structurally simplified analogues is by chemical synthesis.

Total Syntheses of Bryostatins

The unique and complicated structure of the bryostatins, in combination with their biological activities, has attracted extensive attention from the chemistry community to pursue their total synthesis of bryostatins. Bryostatin 7, the first member of the bryostatin family to be made by total synthesis, was reported by Masamune in 1990.[61-63] Evans achieved an equally impressive total synthesis of bryostatin 2 in 1998;[64,65] and two years later in 2000, Nishiyama and Yamamura reported their total synthesis of bryostatin 3.[66-68] Most recently, the Trost group finished the total synthesis of bryostatin 16 and C20-epi bryostatin 7, utilizing methodologies developed by their group to synthesize the B and C pyran rings of bryostatin.[69-73]

The three total syntheses of bryostatin 2, 3 and 7 vary of the reactions to construct the similar moieties. Different strategies were chosen to construct the pyran ring and install the enoate on C13 and C20 positions with desired stereochemistry. Those syntheses also share some common strategies (Figure 1.5). In pursuit of a convergent route to the bryostatins, the pyran rings were prepared separately, then the moieties with pyring rings were coupled together to afford the seco acid intermediates. In orfer to overcome the steric hindrance from the gemi dimthyl group on C18 position, the Julia olefination was utilized to generate the *trans* C16-C17 double bond and connect northern and southern hemisphere moieties. This methodology was taken by all three groups and turned out to be an efficient route. Then a macrolactonization was used to form the 20-membered macrolactone, and further modification on the pyran rings and deprotection afforded the final products.

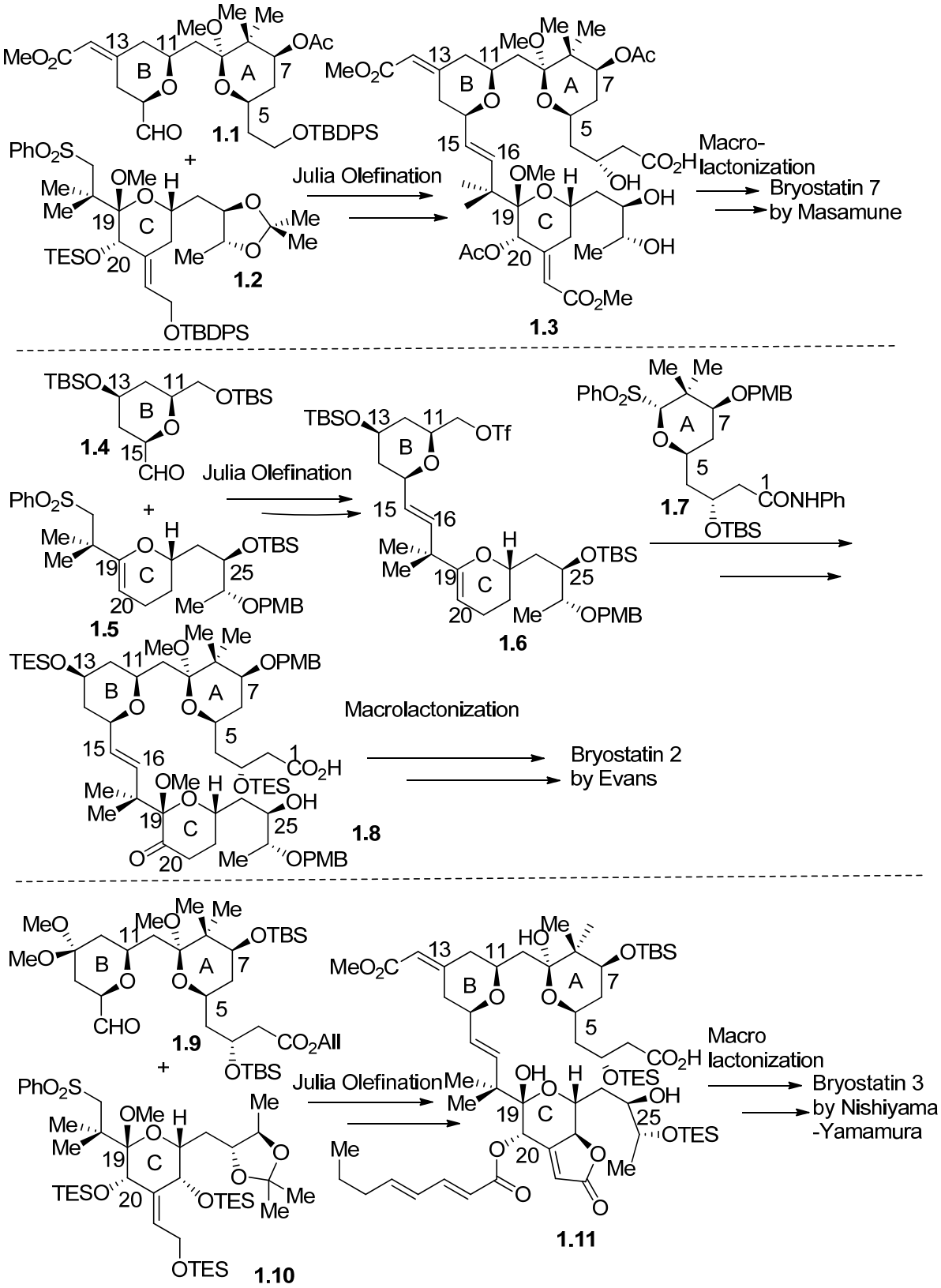
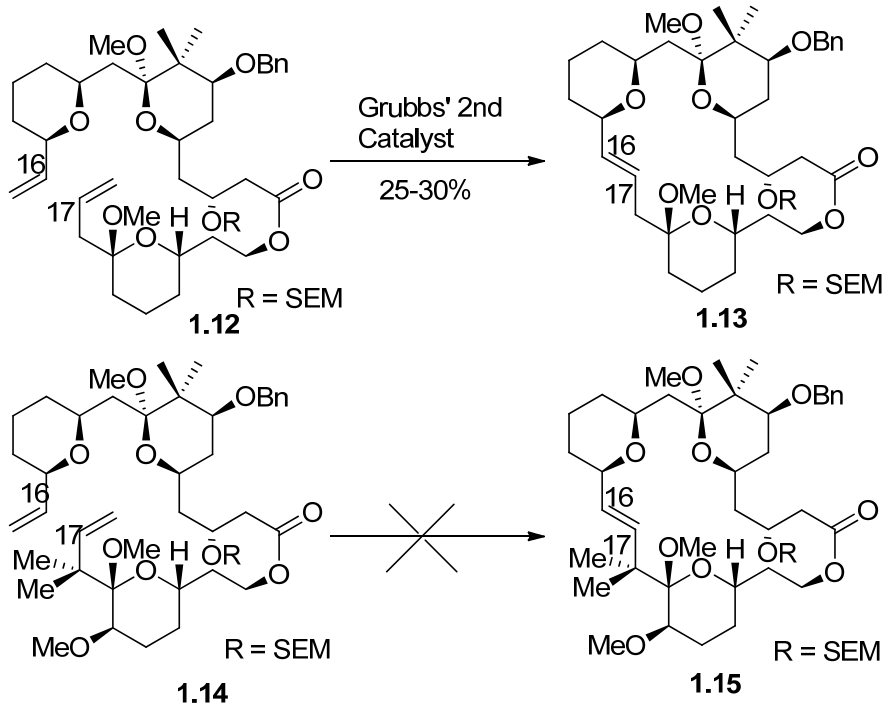


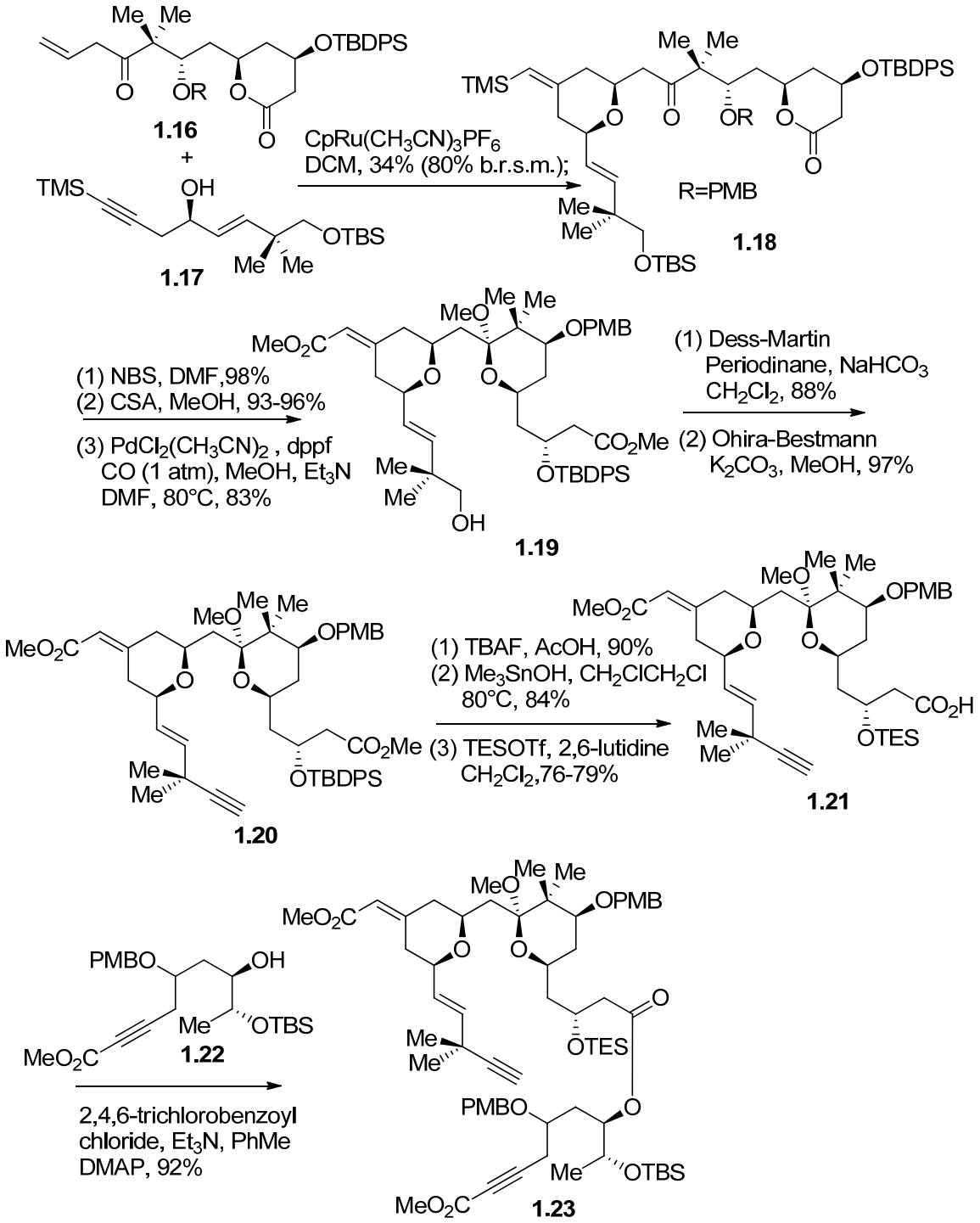
Figure 1.5 Summary of total syntheses of bryostatin 2, 3 and 7

Interestingly, several groups have attempted to cyclize the macrolactone through a ring-closing metathesis between the C16 olefin and C17 olefin during their endeavor to synthesize byrostatin 1.[72,74] Unfortunately, the metathesis reactions failed to provide the desired cyclized products under all the reaction conditions studied, and only a small amounts of the dimers were detected (Scheme 1.1). The failure of ring closing metathesis is believed to be due to the steric hindrance from the *gem*-dimethyl groups on the C18 position.[74]

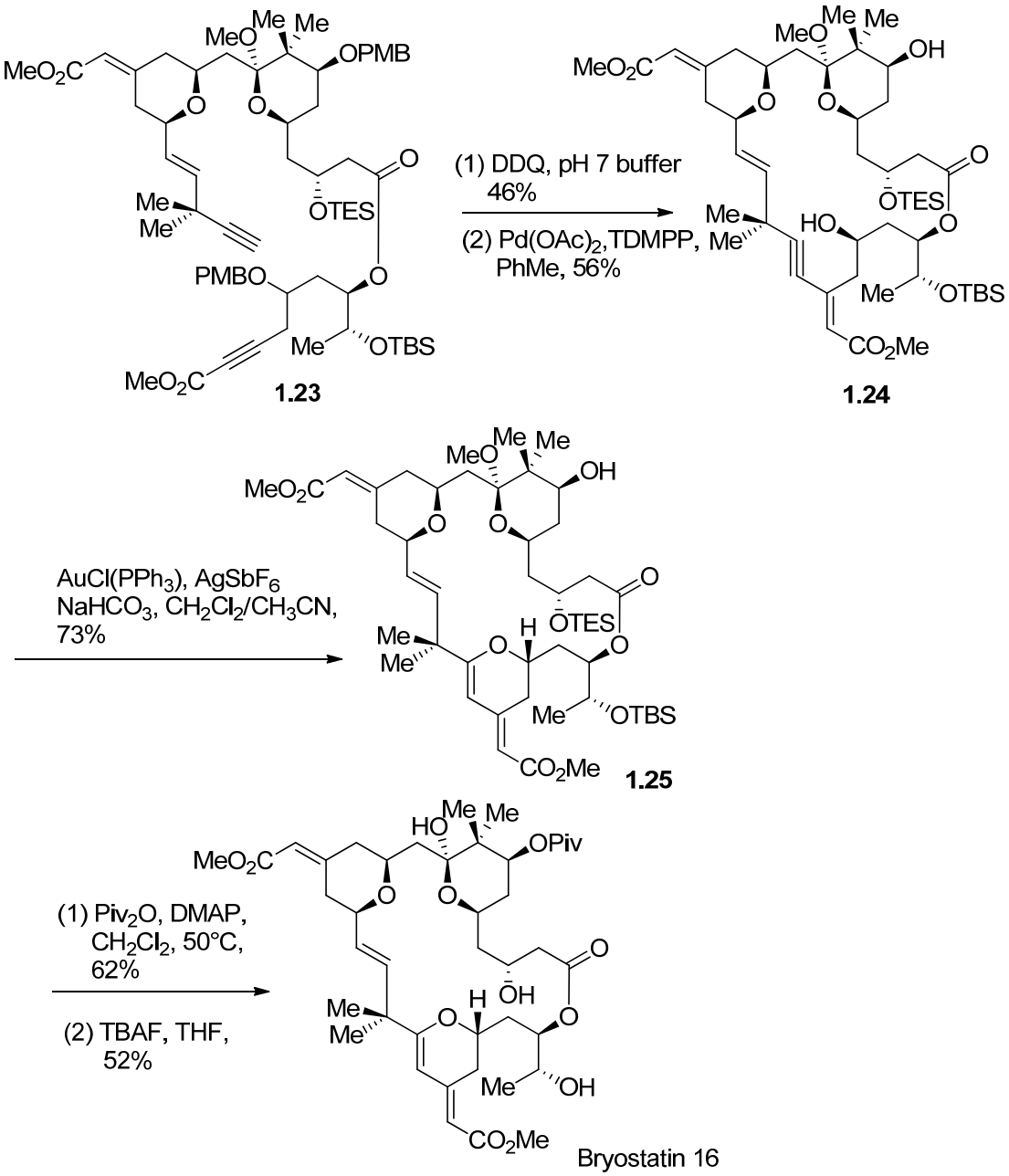


Scheme 1.1 The failed ring-closing metathesis route to close the macrolactone.[74]

The Trost group took a conceptually novel approach to all of the above accomplishments in their synthesis of bryostatin 16 (Scheme 1.2). Intermediates alkene **1.16** and alkyne **1.17**, which were prepared with established routes, were coupled into a pyran **1.18** catalyzed by a cationic ruthenium complex. This impressive transformation, which is proposed to go through a tandem alkyne–enone coupling/Michael addition, generated a 2,6 *syn*-pyran ring with the desired stereochemistry on the exocyclic double bond.[70] The installation of the exocyclic enoate on the B ring was problematic in previous syntheses.[65,68] Trost's approach to the B ring provides a convergent and efficient route to quickly build up the complexity embedded within a natural product like bryostatin. Subsequent bromination of the exocyclic vinyl silane followed by a camphorsulfonic acid catalyzed transesterification/methyl ketalization/deprotection in one pot gave the desired intermediate containing both the A-ring and B-ring substructures. Palladium-catalysed carbonylation installed the methyl enoate to finish all the required modification on the A and B rings to afford alcohol **1.19**. Dess–Martin oxidation of the primary alcohol **1.19** followed by Ohira–Bestmann alkynylation and deprotection provided alkyne **1.20**. Chemoselective hydrolysis of the β-hydroxy methyl ester on the C1 position in the presence of the α, β-unsaturated methyl ester was achieved by using trimethyltin hydroxide, and subsequent protection with TES group on C3 position afforded the carboxylic acid **1.21**. Coupling of **1.21** with alcohol **1.22** using Yamaguchi conditions afford the advanced intermediate **1.23** with all the carbon atoms of bryostatin 16. After the deprotection of the PMB group on C23 postion, attention was focused on the cyclization to form the macrolactone (Scheme 1.3). The failure of ring-closing metathesis in their previous endeavor to bryostatin 1 pushed the Trost group to take a different



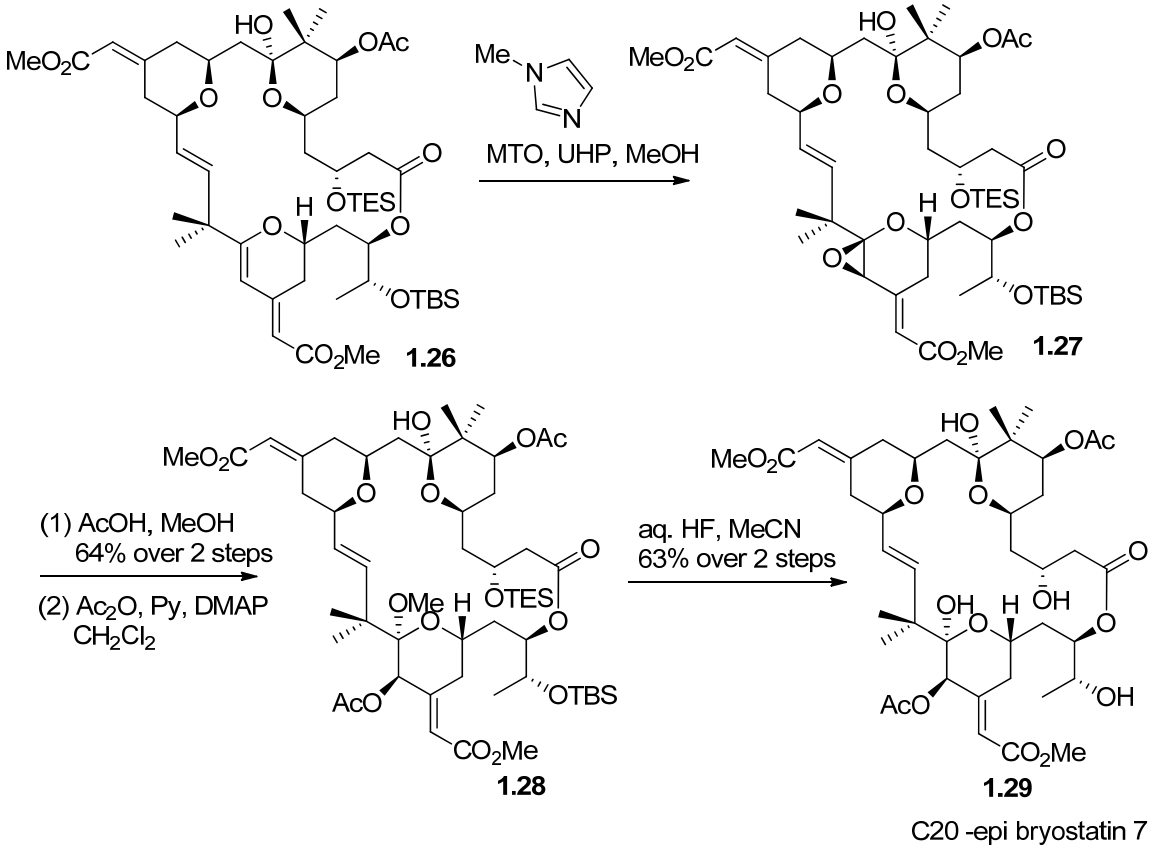
Scheme 1.2 Trost's synthesis of bryostatin 16



Scheme 1.3 The completion of synthesis of bryostatin 16

approach to complete the task. An unprecedented alkyne–ynoate coupling reaction catalyzed by $Pd(OAc)_2$ not only cyclized the macrolactone but also set up the desired stereochemistry on the enoate **1.24**. The use of $[Au(PPh_3)]SbF_6$ was found to deliver a highly regioselective 6-endo pyran product **1.25**. Finally, pivalation of the secondary hydroxy group on the A ring followed by global deprotection completed the synthesis of bryostatin 16.

The Trost group also attempted to further convert bryostatin 16 to other bryostatins (Scheme 1.4). The oxidation of C ring glycal failed to afford the desired product under several standard reaction conditions. Finally, a Re-catalyzed epoxidation, using methyl rhenium trioxide (MTO) as the catalyst and urea-hydrogen peroxide (UHP) as the oxidant, regioselectively oxidized the C19-C20 double bond in intermediate **1.26** to give the epoxide **1.27**, which underwent a methanolysis and acetylation to afford product **1.28**. Unfortunately, the stereochemistry on the C19 and C20 position of **1.28** is opposite to that of the natural bryostatins. Trost rationalized the unusual stereoselectivity due to the approach of the Re catalyst from the less hindered face of the C-ring at the epoxidation stage to minimize the steric effect from the gem-dimethyl group on the C19 position. The following deprotection lead to C20-epi bryostatin 7 (**1.29**). In order to prepare natural bryostatin 7, the C20 alcohol was oxidized to a ketone and several reducing reagents were screened. The best selectivity is obtained with a CBS reduction, which gave a 1:2 mixture, favoring the undesired stereochemistry on C20 position. The diastereomer mixtures were separated, and bryostatin 7 was finally prepared after acetylation and deprotection.



Scheme 1.4 The synthesis of C20-epi bryostatin 7

Additionally, there are also several other groups working on the total synthesis of bryostatins, which include the formal synthesis of bryostatin 7 by the Hale group,[75,76] and partial syntheses by Burke,[75,77,78] Krische,[79,80] Thomas,[74,81] Vanderwalle,[82-84] Kiyooka,[85] Roy,[86] hoffmann,[87] Janda,[88] and our group.[89-91] Each total synthesis of a bryostatin demonstrates an accomplishment of great challenge and is a masterpiece of synthetic organic chemistry. Due to the molecular size and its structural complexity, it will be more practical to pursue simplified structural analogues that retain or improve upon

bryostatin's pharmaceutical profile. This approach could eventually provide a solution to fit the needs of biological research and future clinical trials.

Wender's Bryostatin Analogue Study

The Wender group has been working on the design, synthesis and biological studies of bryostatin analogues since the 1980s. Based on the fact that the phorbol esters, diacyl glycerols, and bryostatins, which are structurally different, bind competitively to the same activator C1 domain of PKC, Wender envisioned that these compounds would be expected to possess a common pharmacophore, i.e., a similar three-dimensional array of homologous functional groups in their bound or active conformations.

First, the Wender group used a computer comparison of x-ray and/or calculated structures of the ingenol, teleocidin, gnidimacrin, and DAG, classes of protein kinase C activators, to identify the isospatial functional groups and hydrophobic regions that constitute the putative PMA pharmacophore.[92] This approach suggested a critical role for the C4, C9, and C20 oxygens of the phorbol esters. The structural comparison was further extended for bryostatin 1.[93] Quantification of the structural relationships among bryostatin 1, phorbol ester, and (*S*)-1,2-diacyl-*sn*-glycerol was accomplished by a computer-assisted comparison of the respective pharmacophoric oxygens of those three protein kinase C activators. Since the relative coordinates of the rotationally mobile C25-C26 hydroxyethyl atoms can vary, the relative energies of all conformations resulting from rotation about the C25-C26 bond were calculated (MMP2).

The results indicated that the C26 oxygen of the bryostatins, together with the C1 and C19 oxygens, gave an excellent spatial correlation with this model, with a root-mean-

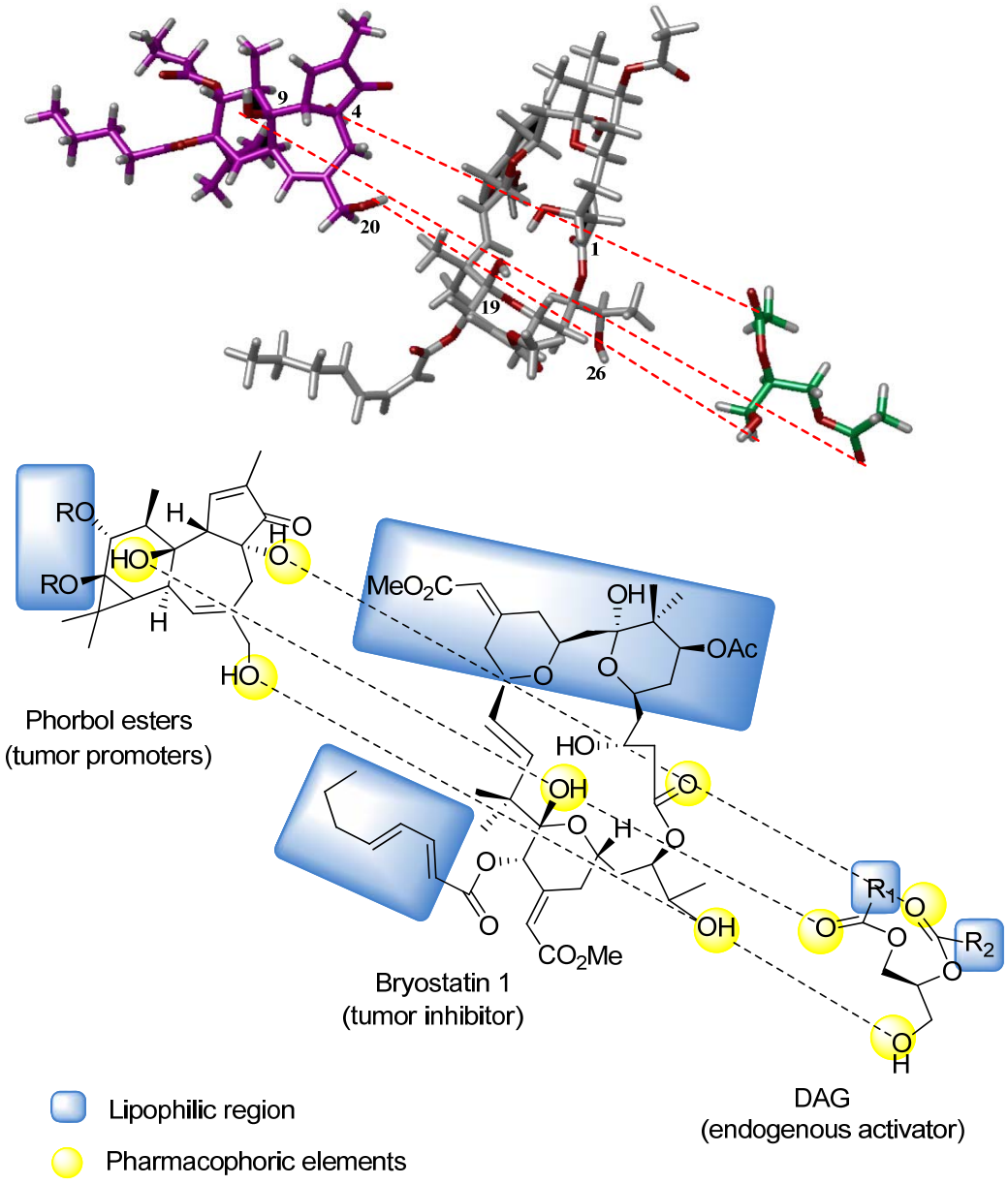


Figure 1.6 The pharmacophoric groups among DAG, PMA and bryostatin 1

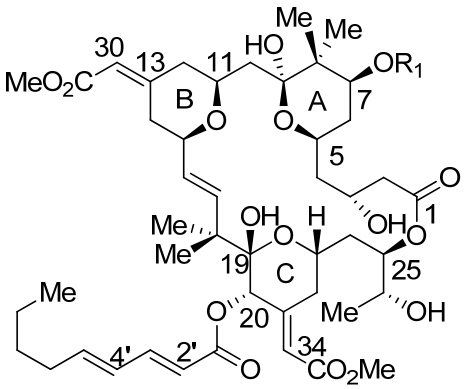
square deviation of 0.16 Å. The extension of the phorbol ester pharmacophore model to the bryostatins and its agreement with the structure-activity relations for the bryostatin class of compounds provide additional support for the validity of the model (Figure 1.6).[94]

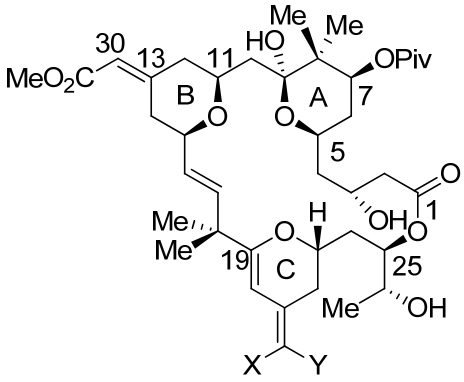
In cooperation with the Pettit group and the Blumberg group, the Wender group also systematically studied the structure-activity relationship of bryostatins based on the binding affinity, which was determined by the measurement of competitive inhibition of [26-^{3}H]bryostatin 4 binding with PKC (Table 1.1).[94] Their observation showed that different substituted groups on C7 and C20 position of bryostatins have a limited effect on the binding affinity. The chemically modified C13-C30 epoxide bryostatin 4 analogue[10] has a little better binding affinity with PKC. Analogues in which both the C13-C30 and side chain on C20 are hydrogenated showed modestly reduced affinities, while the analogue in which C13-C30, C21-C34 and side chain on C20 are hydrogenated showed markedly reduced affinities. Elimination of the C19 hydroxyl group or inversion of stereochemistry at C26 has a more pronounced effect on affinity. Finally, acetylation at C26 eliminates significant binding affinity. Viewed collectively, these observations suggest that the binding of the bryostatins is only modestly affected by changes in the northern hemisphere or side chain on C20, while the modifications in the southern hemisphere dramatically alter the binding affinity.

All the above results lead to the hypothesis proposed by the Wender group that the C4-C16 moiety in bryostatin 1 acts as a spacer domain, while the C19-C26 domain acts as a recognition domain during the binding with C1 domain within PKC. This hypothesis has been applied in the design of simplified, fully synthetic bryostatin

Table 1.1 Comparison of binding affinities to PKC of bryostatins (Bryo)

and their derivatives





Bryo 16: X =H, Y = CO_2Me
Bryo 17: X = CO_2Me, Y = H

Compounds	Ki (*n*M)	n
Bryo1	1.35±0.17	5
Bryo2	5.86±1.13	3
Bryo3	2.75±0.05	2
Bryo4	1.30±0.19	2
Bryo5	1.04±0.10	2
Bryo6	1.18±0.29	2
Byro7	0.84±0.07	2
Bryo8	1.72± 0.10	2
Bryo9	1.31±0.00	2
Bryo10	118±2	2
Bryo16	188±7	N/A
Bryo17	0.54±0.07	N/A
Bryo4 13, 30 epoxide	>>100	N/A
Bryo4 26 acetate	32.6±6.6	N/A
Bryo1 epi-26	9.61±0.94	N/A
Bryo2 13,30, 2',3',4',5'-hexahydro	473±96	N/A
Bryo2 13,30, 21, 34, 2',3',4',5'-octahydro		N/A

analogues (Figure 1.7). The first de novo synthesis of a bryostatin analogue was reported by the Wender group in 1998.[95] Compared with bryostatin 1, the first analogue **1.30** retained of all the functionality of bryostatin 1 on the southern hemisphere, while the northern hemisphere of the analogue had been simplified into a pyran ring and a six-membered cyclic acetal. Functionality along the C7-C13 periphery of bryostatin 1 was completely eliminated, and C14 was replaced by an oxygen to facilitate synthesis. The unsaturated side chain on C20 of bryostatin 1 was replaced by a saturated side chain on the same position of bryostatin analogue**.**

The retrosynthetic plan to the analogue **1.30** is outlined in Figure 1.8. The cyclic acetalization will both form the cyclic acetal and close the macrolactone. The precursor **1.31** was expected to be prepared by an intermolecular esterification between carboxylic acid **1.32** and alcohol **1.33**. This convergent plan did not only provide analogue in a highly efficient manner, but also provide an opportunity to approach analogue libraries

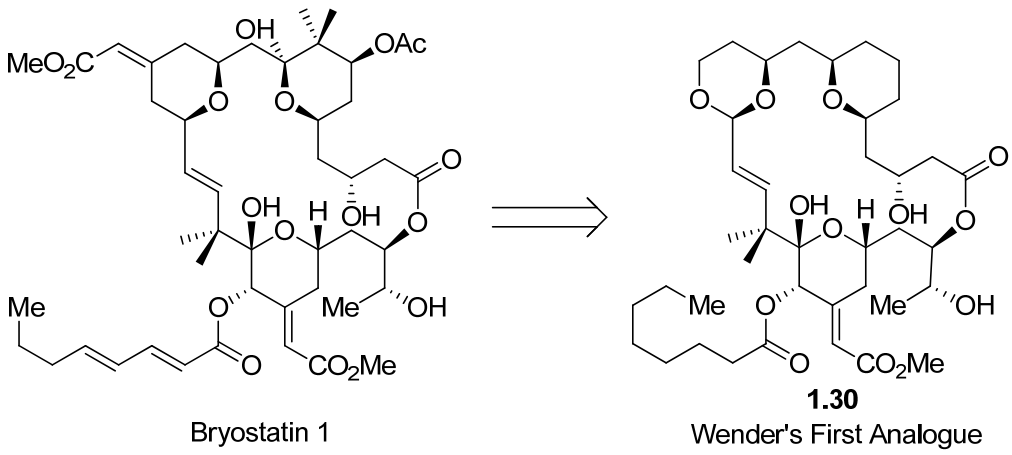


Figure 1.7 Bryostatin 1 and Wender's original analogue

through combinatorial synthesis involving the coupling of recognition domain moiety **1.33** with various readily available acid-acetals.

The synthesis of aldehyde **1.33** started with (*D*)-methyl lactate **1.34**, which was protected with a benzyl group (Scheme 1.5). Exposure of lactate to DIBAL-H at -78 °C was able to deliver the partially reduced aldehyde product. A chelation-controlled allylation in the presence of $SnCl_4$ as the Lewis acid was chosen to set the stereochemistry on C25 position to afford homoallylic alcohol **1.35**, which was protected with a PMB group and oxidatively cleaved by ozonolysis to give aldehyde **1.36**.

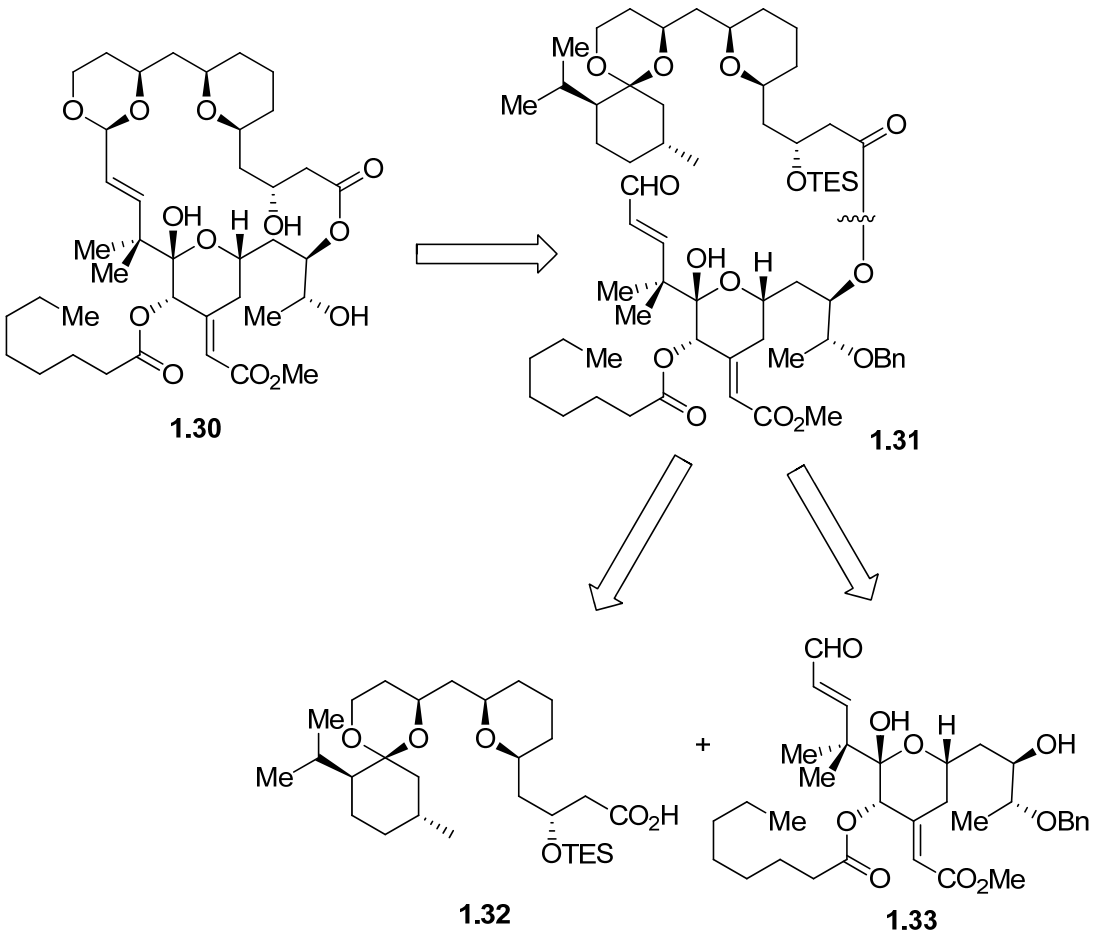


Figure 1.8 The retrosynthesis of Wender's first bryostatin analogue

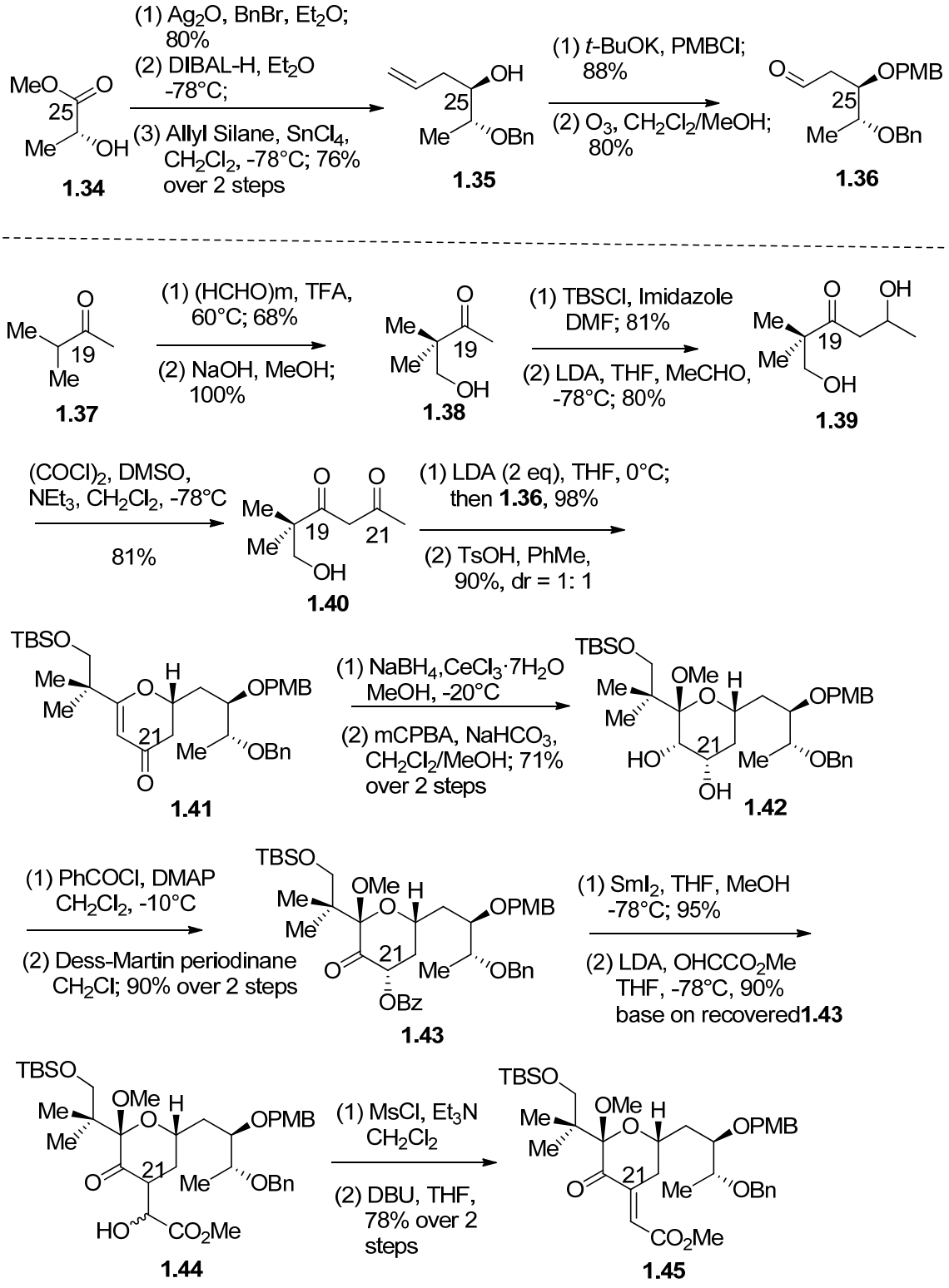
Trifluoroacetic acid catalyzed aldol reaction between ketone **1.37** and paraformaldehyde, followed by hydrolysis delivered alcohol **1.38**, which was protected as a TBS ether. A second aldol reaction with ethanal generated alcohol **1.39**, which was oxidized to afford the 1,3-diketone **1.40**. A third aldol between the enolate dianion of diketone **1.40** and aldehyde **1.36** lead to a *β*-hydroxy ketone, which was subjected to *p*-toluenesulfonic acid to promote a cyclization and dehydration to afford the pyranone product **1.41** with a 1:1 ratio at C23. The desired β-isomer was easily separated and reduced under Luche conditions and the resulting glycal was epoxidized with *m*CPBA in the presence of MeOH to afford a C19-methoxylated C20, C21-diol **1.42**. Selective benzoylation of the C21 equatorial alcohol followed by oxidation of the remaining C20 hydroxyl group with Dess-Martin periodinane provided benzoate **1.43.** Treatment of **1.43** with SmI_2 selectively deoxygenated on C21 to give a ketone. which underwent an aldol condensation with methyl glyoxylate to give product **1.44**, and the following mesylation and elimination successfully installed the desired *E*-exocyclic unsaturated ester at C21, providing enone **1.45**.

The enone **1.45** was reduced under Luche reaction conditions to afford the C20 axial alcohol exclusively, which was esterified with octanoic acid to afford compound **1.46** (Scheme 1.6). Completion of the target fragment, requiring a demanding two carbon homologation at C17, which proceeded through removal of the TBS group with HF/pyridine and oxidation of the resulting alcohol with Dess-Martin periodinane to give aldehyde **1.47**. This hindered aldehyde was found to react with allyldiethylborane followed by Ac_2O to generate an inconsequential mixture of acetates **1.48** in high yield. Dihydroxylation of the terminal olefin with catalytic OsO_4 (NMO co-oxidant) afforded

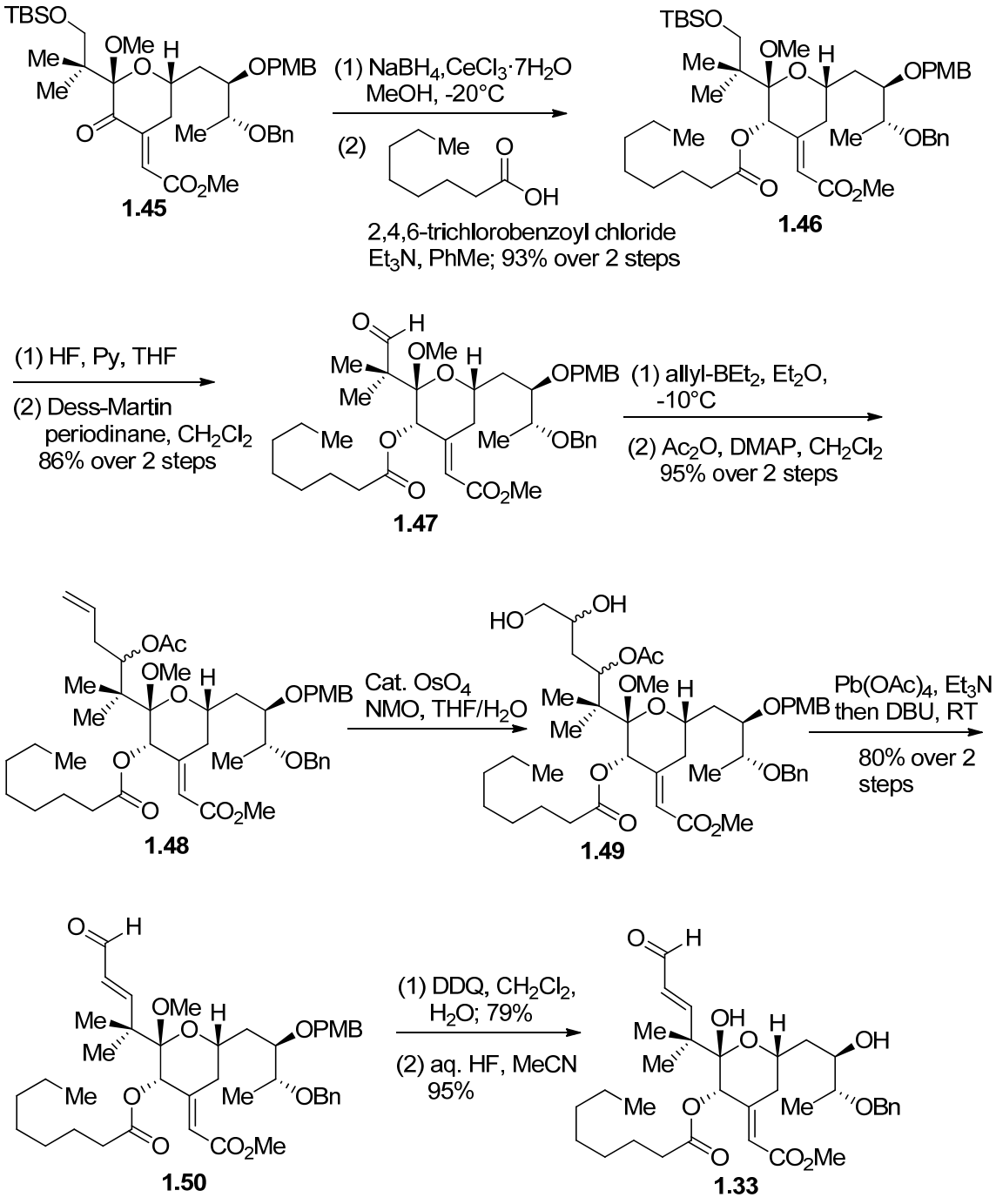
the diol **1.49** and $Pb(OAc)_4$-mediated glycol cleavage transformed the diol **1.49** into enal **1.50**. Exposure of **1.50** to DDQ selectively liberated the C25 alcohol, then treatment with aqueous HF, gave the target hemiketal **1.33**.

The synthesis of carboxylic acid **1.32** started with a stereoselective resolution of TMS protected 1,3,5-pentantriol **1.51** with (-)-menthone and TMSOTf. The resulting mixtures were easily separated by flash column chromatography and the desired alcohol **1.52** subjected to Dess-Martin periodinane to afford the aldehyde **1.53** (Scheme 1.7). A hetero-Diels-Alder reaction between aldehyde **1.53** and Danishefsky's diene lead to the formation of a pyranone, which was regioselectively reduced by a Luche reaction to give pyran **1.54**. A Claisen rearrangement was chosen to set the stereochemistry at C5 to give aldehyde **1.55**, and the resulting double bond was reduced by a hydrogenation catalyzed by palladium. A Brown asymmetric allylation set up the C3 stereocenter, and the resulting homoallylic alcohol was protected with a TBS group to afford **1.56**. The olefin was transformed into an acid by the combination of $KMnO_4$ and $NaIO_4$. The TBS group was swapped with a TES group in a two steps manner to give acid **1.32**.

The acid **1.32** and alcohol **1.33** were coupled together using Yamaguchi's conditions to give **1.31**, then the TES group on the C3 position was removed by HF/Py. Finally, treatment with Amberlyst-15 promoted the formation of the macrocycle and completion of bryostatin analogue **1.30** (Scheme 1.8). The C26 hydroxyl group was regioselectively acylated to afford the C26-acetate analogue **1.57**.

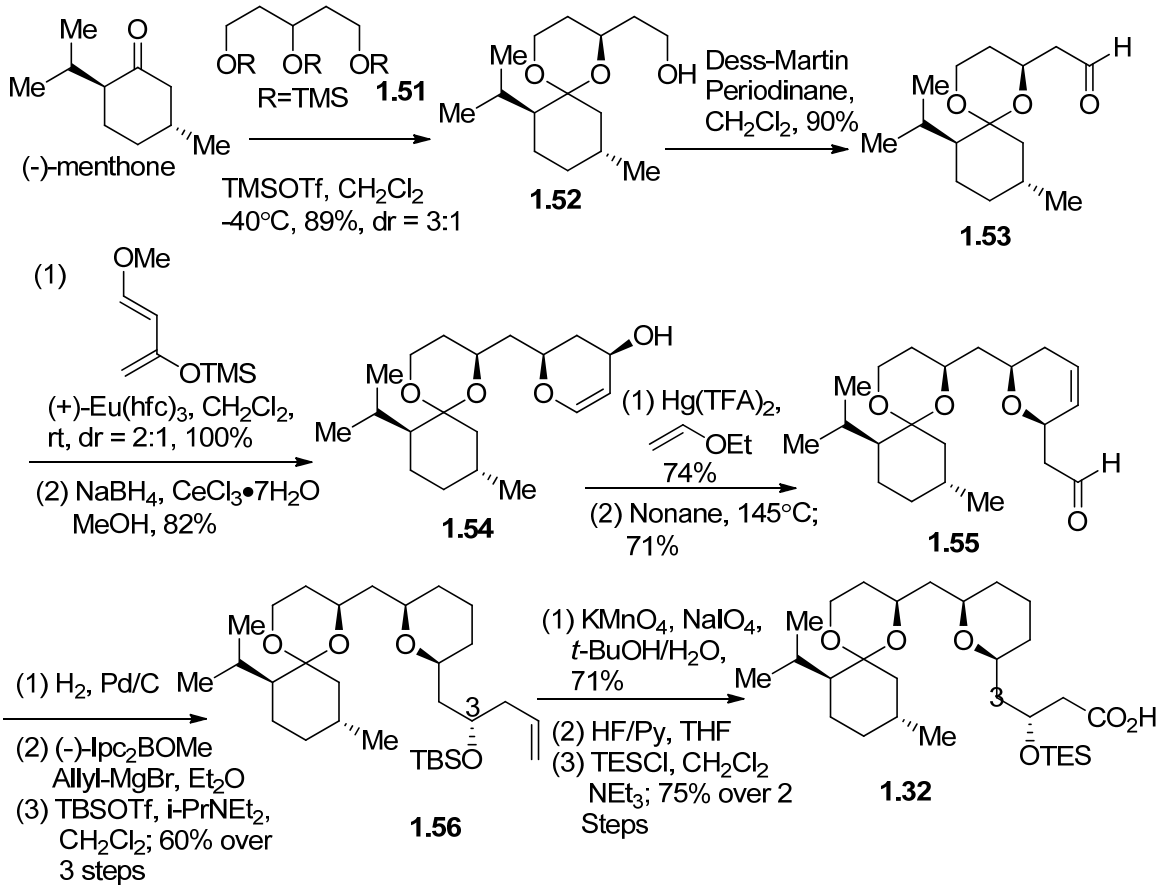


Scheme 1.5 Synthesis of recognition domain of first bryostatin analogue

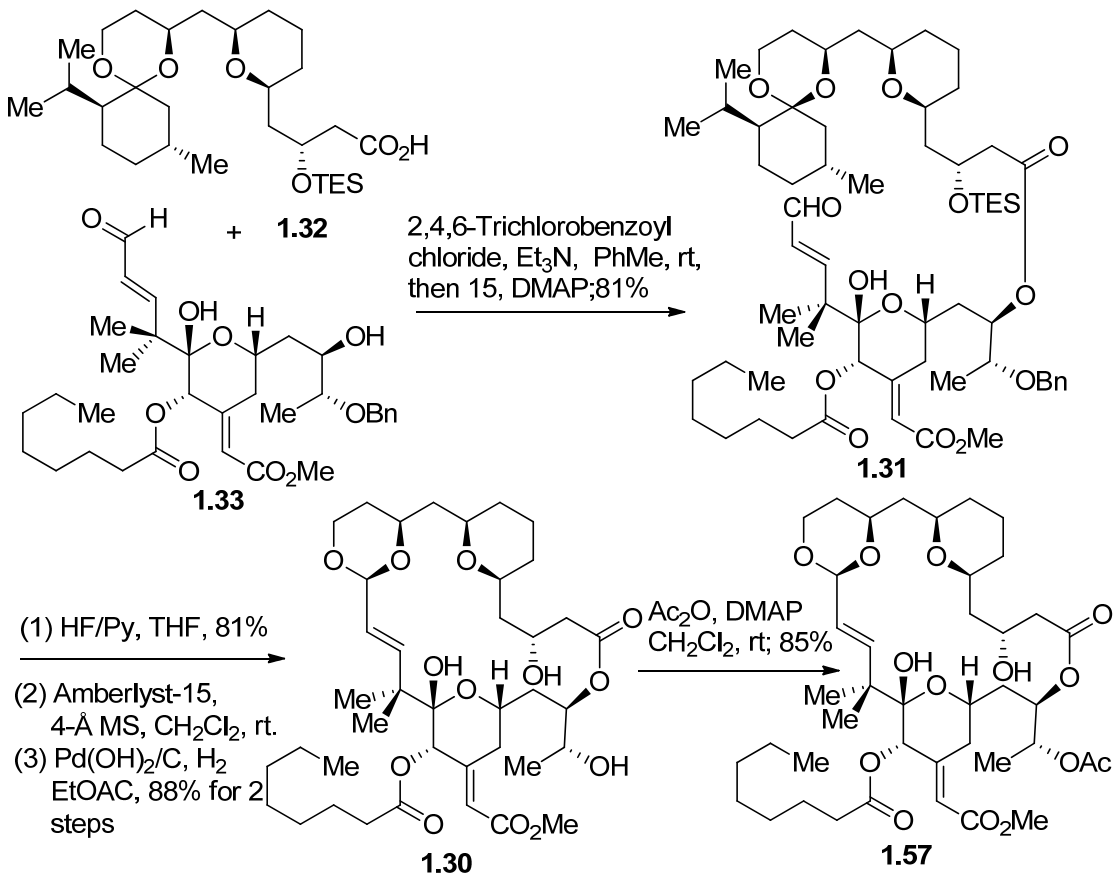


Scheme 1.6 The synthesis of recognition domain of first bryostatin analogue

The analogues **1.30** and **1.57** were evaluated for their ability to bind to a mixture of rat brain PKC isozymes. The results show that the analogue **1.30** has a similar binding affinity with PKC as does bryostatin 1. (Analgoue **1.30**, K_i = 3.4 ± 0.6 *n*M; bryostatin K_i = 1.37 ± 0.17 *n*M).[95] The C26 acetate analogue **1.57** lost its binding affinity with PKC (K_i >> 100 *n*M), which confirmed the importance of the C26 hydroxyl group in binding with PKC. The growth inhibitory activities of the analogues **1.30** against several known cancer cell lines indicated that the analogue **1.30** could inhibit the growth of cancer cells in nanomolar concentration (Table 1.2).[94]



Scheme 1.7 Synthesis of spacer domain of first bryostatin analogue



Scheme 1.8 The completion of bryostatin analogue **1.30**

Table 1.2. *In vitro* cell growth inhibitory activity of analogue **1.30**

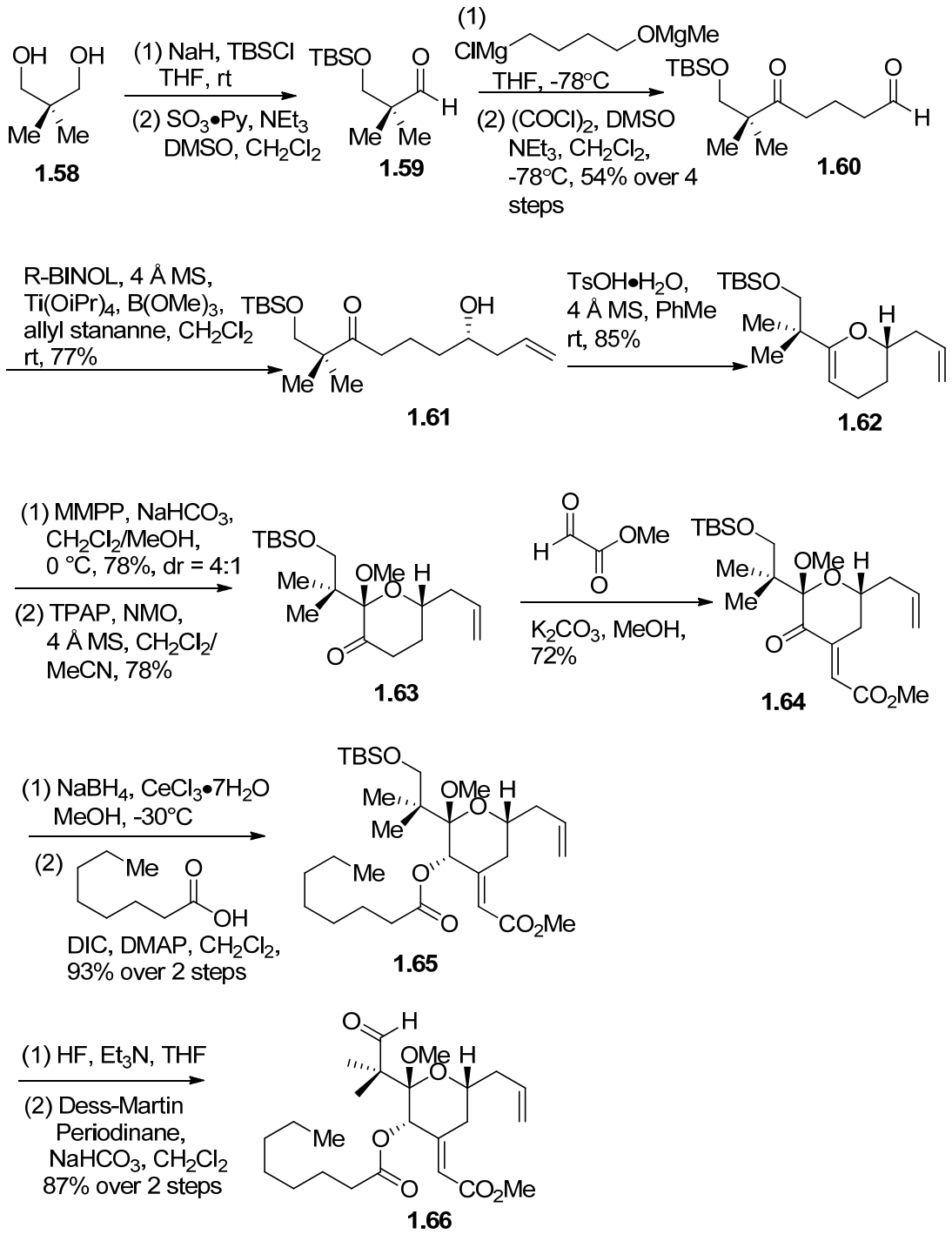
Human cancer cell line	GI_{50} (μg/ml)
BXPC-3 (pancreas)	6.0×10^{-3}
NCI-H460 (lung-nonsmall cell)	2.3×10^{-1}
FADU (pharynx)	1.8×10^{-3}
DU-145 (prostate)	1.7×10^{-1}

The Wender group also studied the solution conformation of bryostatin analogue **1.30**.[94] The high field one- and two-dimensional proton NMR spectra of analogue **1.30** showed a close correlation between the ^{1}H chemical shifts and multiplicities in $CDCl_3$ with those of bryostatin 10 throughout most of the putative pharmacophoric region (C16-C23). Phase-sensitive nuclear Overhauser effect spectroscopy (NOESY), total correlation spectroscopy (TOCSY), and double quantum-filtered correlated spectroscopy (DQCOSY) spectra of analogue **1.30** in C_6D_6 were analyzed to determine the identity and categorical distances between protons throughout the structure. The results were applied to a constrained gas-phase molecular dynamics simulation, and followed by minimization. Among the conformers that were identified, six were within 2 kcal/mol of the global minimum. The lowest energy conformers satisfied all the nuclear Overhauser effect constraints and compared favorably with the published crystal structure of bryostatin 1 as well as the solution structure of bryostatin 10. Superpositioning of the lowest energy conformer and the crystal structure of bryostatin 1 (comparison of all atoms except hydrogen) gave a rms deviation of 0.506 Å, while the rms deviation calculated by superimposing the pharmacophoric atoms (C16-C23 region) of the lowest-energy conformer onto their counterparts in bryostatin 1 is 0.313 Å, indicating a remarkably good correlation between the two in their recognition region.

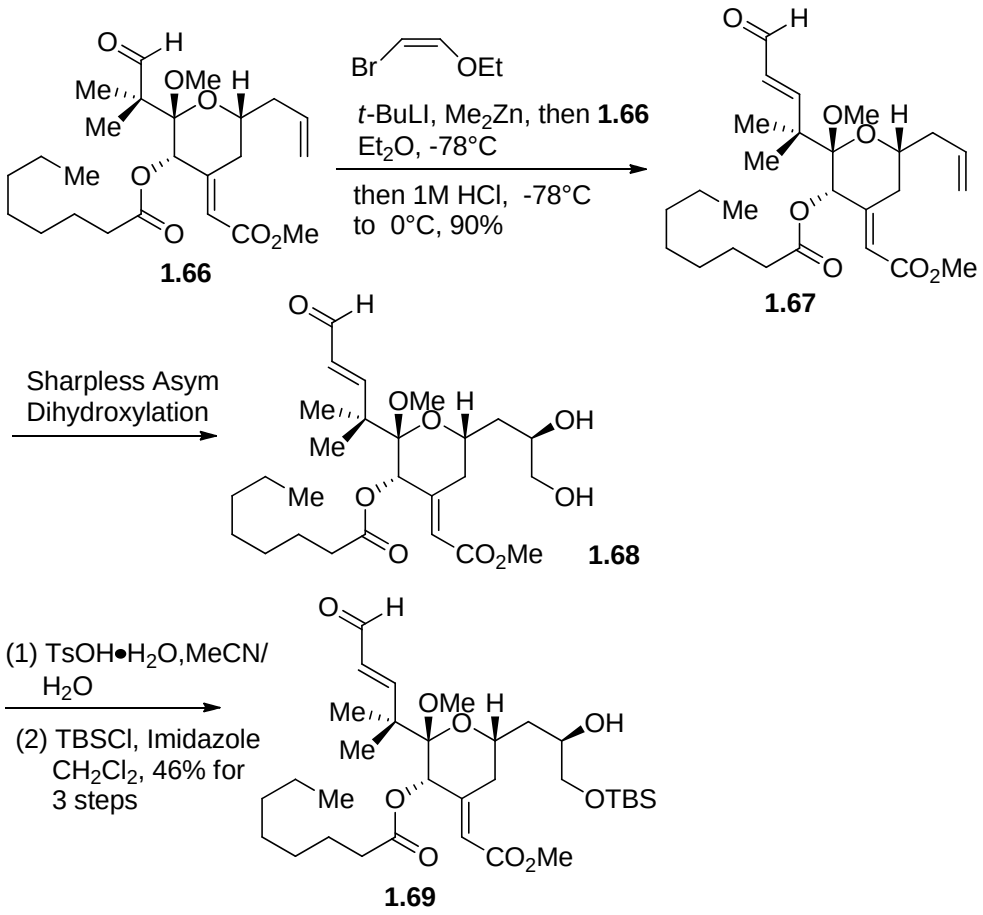
All the results from the binding affinity, biological studies and computational analysis support Wender's hypothesis of bryostatin analogue design, which also encouraged them to further improve their route by simplifying and diversifying these new leads to help elucidate the molecular basis for bryostatin's activity.

In 2002, the Wender group published their second generation synthesis of bryostatin analogues.[96] The synthesis of the C15-C26 recognition domain began with the monoprotection of diol **1.58** as a TBS ether and the resulting alcohol was oxidized by Parikh-Doering oxidation to generate aldehyde **1.59** (Scheme 1.9). Reaction of **1.59** with the Grignard reagent derived from 4-chloro-1-butanol followed by Swern oxidation afforded aldehyde **1.60**. Keck asymmetric allylation of aldehyde **1.60** provided homoallylic alcohol **1.61**. Dehydrative cyclization of **1.61** promoted by *p*-toluenesulfonic acid afforded the glycal **1.62**, which underwent an epoxidation and in situ methanolysis to yield a mixture of diastereomers, the major of which was oxidized to ketone **1.63**. Conversion of ketone **1.63** to enone **1.64** was accomplished in one step by treatment with K_2CO_3 and methyl glyoxylate in MeOH at room temperature as compared to the three step sequence in the first generation synthesis. A highly diastereoselective reduction of enone **1.64** followed by esterification afforded ester **1.65.** Deprotection of the TBS group on C17 followed by oxidation gave aldehyde **1.66**.

Because aldehyde **1.66** is both sterically hindered and susceptible to deprotonation at the C22 position, chain extension using this intermediate proved challenging. A reaction using a vinyl zincate derived from (*Z*)-1-bromo-2-ethoxyethene was found to be effective for the homologation of the carbon chain to afford the enal **1.67** (Scheme 1.10).[96] Sharpless asymmetric dihydroxylation conditions were used to convert **1.67** to diol **1.68** with 2.5:1 diastereoselectivity. The diastereomers were separated following hydrolysis of the C19 ketal and selective protection of the primary alcohol on the C26 position gave the aldehyde **1.69**.

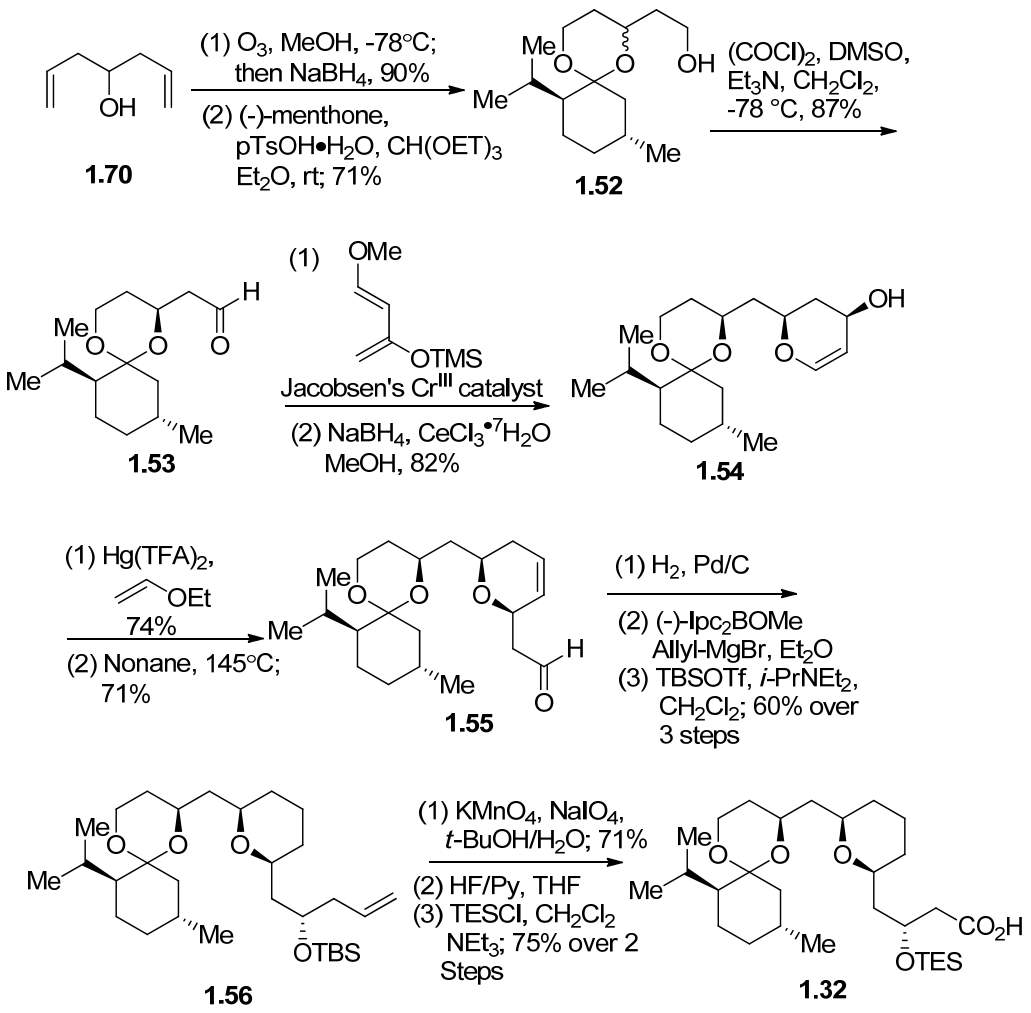


Scheme 1.9 The second generation synthesis of recognition domain



Scheme 1.10 The second generation synthesis of recognition domain

The synthesis of the C1-C13 spacer domain began with ozonolysis and in situ reduction of **1.70**, which produced pentane-1,3,5-triol in a manner superior to that of previous methods (Scheme 1.11). Desymmetrization of the resulting triol via acetal formation with (-)-menthone and subsequent oxidation yielded a mixture of aldehydes **1.52**, which were separated by flash column chromatography. A hetero Diels-Alder cycloaddition between aldehyde **1.52** and Danishefsky's diene using Jacobsen's tridentate Cr (III) catalyst provided a pyranone with exceptional selectivity (33:1). At this point, their second generation synthesis follows the same route discussed in their first generation synthesis.



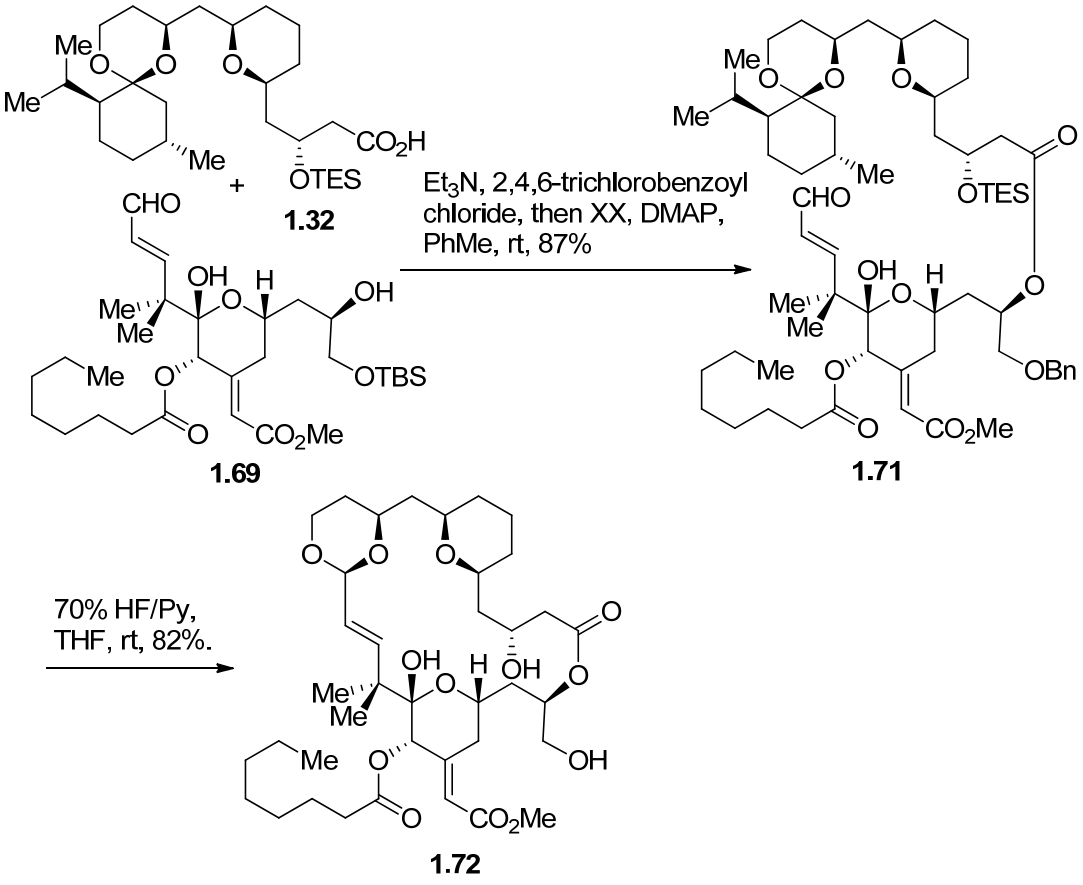
Scheme 1.11 The Second Generation Synthesis of Recognition Domain

The carboxylic acid **1.32** and alcohol **1.69** were coupled together with the Yamaguchi protocol to give product **1.71** (Scheme 1.12). Treatment with HF/Py not only removed the silyl groups, but also promoted the transacetalization to close the macrocycle, and set the C15 stereocenter under thermodynamic control, leading to the final product **1.72**.

The bryostatin analogue **1.72**, which does not have the C27 methyl group when compared with the first bryostatin analogue **1.30**, shows a better binding affinity with

PKCs (K_i = 0.25 *n*M). When tested in vitro against various human cancer cell lines, both analogue **1.30** and **1.72** displayed greater potency than bryostatin 1. Analogue **1.72** outperformed bryostatin 1 at inhibiting the growth of cancer cells, in some cases by up to three orders of magnitude.[97]

The PKC translocation test indicated analogues were able to induce translocation of PKC as did bryostatin 1.[98] The treatment with analogue **1.72** and **1.30** were able to cause the translation of PKC to the membrane, which could be visualized under microscopy by green fluorescent protein fused PKC in live cells.



Scheme 1.12 The Second Generation Synthesis of Bryostatin Analogue **1.72**

RasGRP is a protein family with C1 domain that appears to play a critical role in T-cell receptor signaling. Activation of RasGRP appears to be responsible for some of the immune system effects previously attributed to PKC. Once RasGRP is activated and translocated to the plasma membrane, it activates Ras and initiates a series of downregulation relate to immune response. When analogues **1.72** and **1.30** were tested in HEK-293 cell assays measuring RasGRP1 activation, the compounds displayed the activities similar to bryostatin 1.[99]

In summary, by utilizing their convergent methodology, the Wender group was able to systematically investigate the structure and activity relationship (SAR) through the synthesis of bryostatin analogues (Figure 1.9).[96,100-105] All the bryostatin analogues show high potency of binding with PKCs.

Wender concluded his bryostatin analogue work into a new term as function-oriented synthesis (FOS) and illustrated its importance to drug discovery.[97,106,107] He stated that natural products are not "designed" for human therapeutic use and as a consequence often have undesired side effects. By focusing on target-specific function, FOS can be used to minimize off-target activities and to enhance beneficial activities, such as optimize formulation, ADME, and pharmacokinetic performance, thereby voiding problems exhibited by many natural products. Most importantly, it can address the concern that some natural products are too complex to make practically by replacing them with structurally simplified analogues.

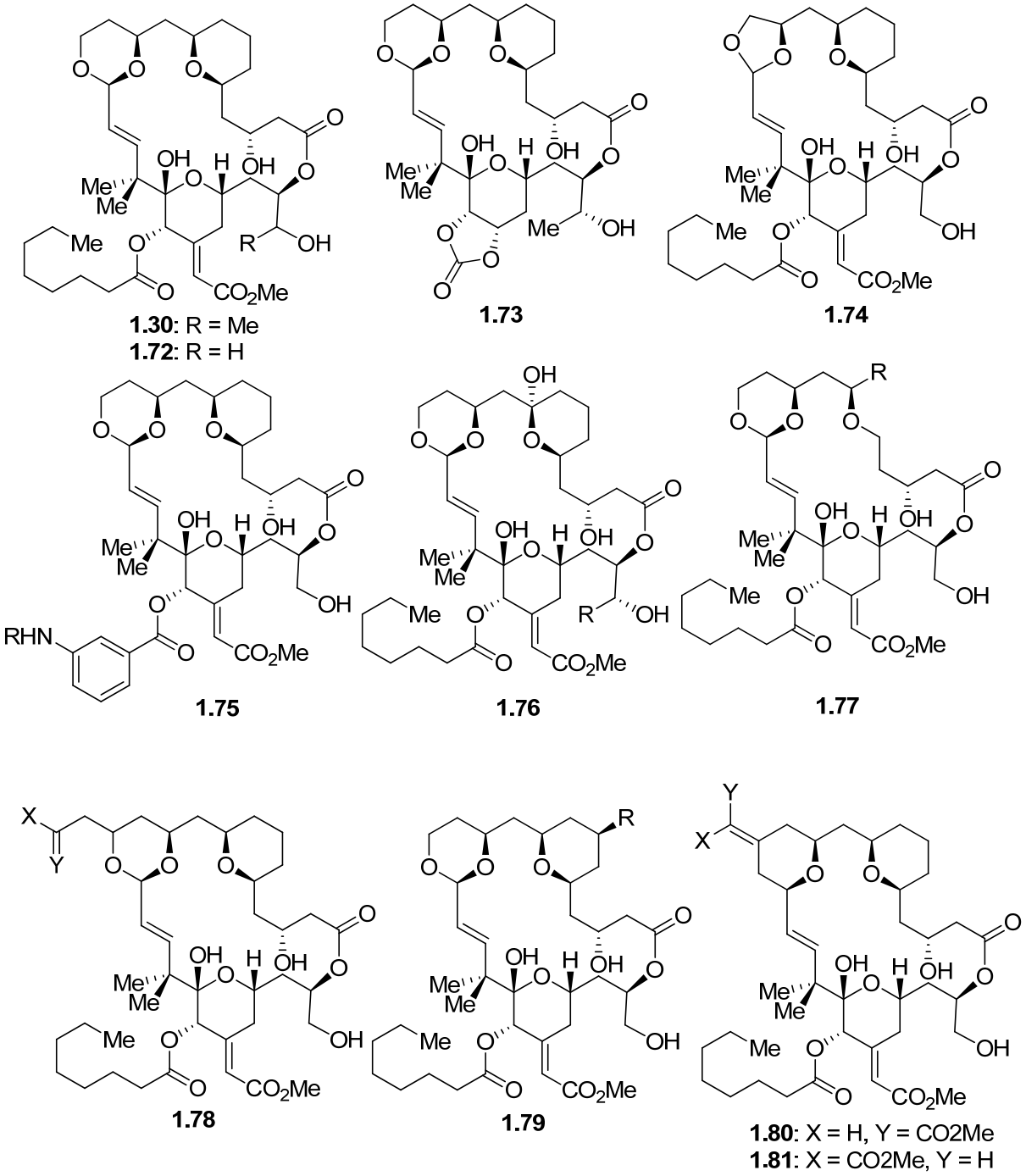


Figure 1.9 Library of Wender's Bryostatin Analogues

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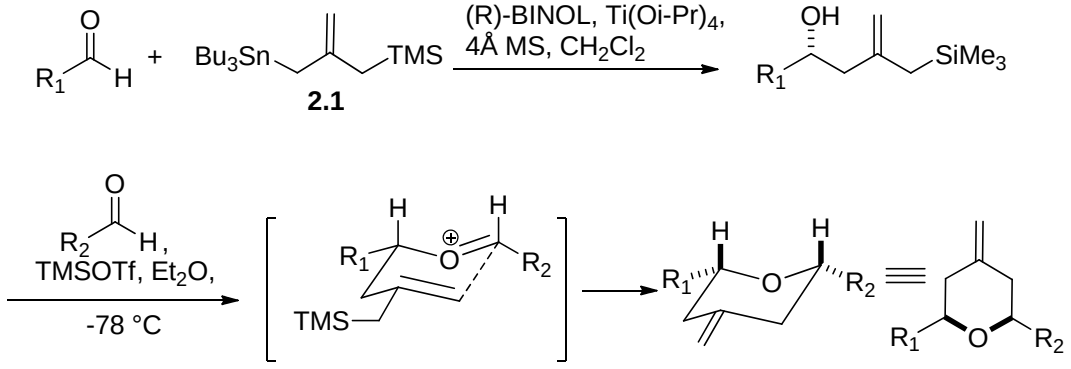
CHAPTER 2

STUDY OF THE EFFECT OF C7 ACETATE AND C13 ENOATE ON BIOACTIVITIES OF BRYOSTATIN 1 THROUGH THE SYNTHESIS OF BRYOSTATIN ANALOGUES

Keck's Bryostatin Analogue Study

The Keck group has been involved in the synthesis of bryostatin 1 and analogues since the 1990s. The methodology termed as pyran annulation developed by Dr. Covel and Dr.Yu in the Keck group provides an efficient and flexible route to prepare 2,6-di-substituted pyrans in a two step manner (Scheme 2.1).[1] The first step involves a catalytic asymmetric allylation (CAA) between an aldehyde and 2-trimethylsilylmethallyl stannane **2.1** forming the corresponding *β*-hydroxyallylsilanes. The second step is a Prins type cyclization involving treatment of the hydroxyallylsilane with a second aldehyde and TMSOTf at -78 °C, which subsequently undergoes cyclization to afford the *cis*-2,6-disubstituted-tetrahydropyran in high yields and as a single diastereomer.

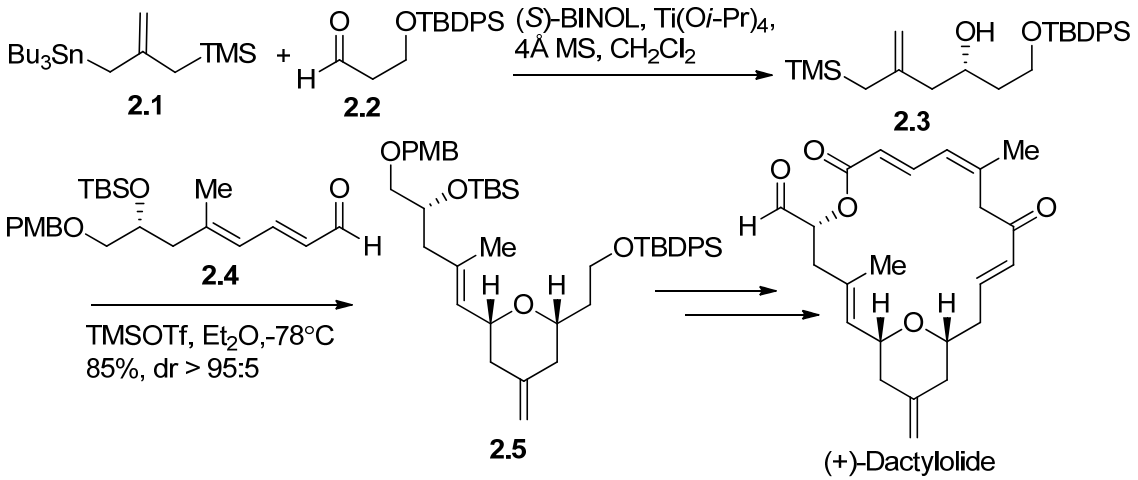


Scheme 2.1 Asymmetric Pyran Annulation

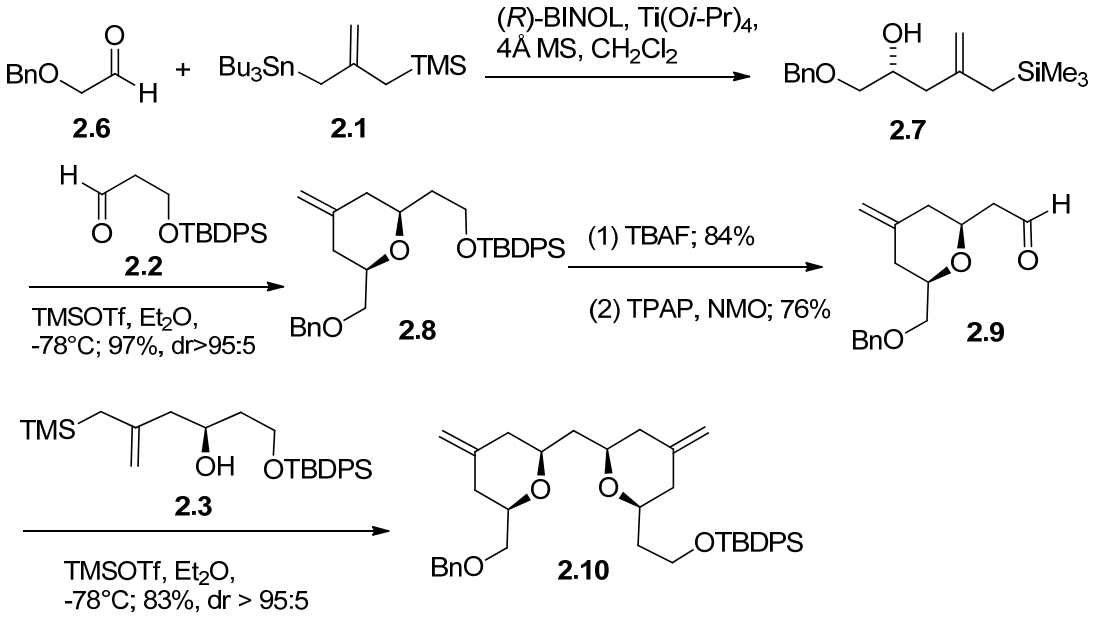
Dr. Sanchez accomplished the total synthesis of dactylolide by using the pyran annulation to construct the 2,6-syn pyran ring (Scheme 2.2).[2] The CAA reaction between stannane **2.1** and aldehyde **2.2** gave hydroxyallylsilane**2.3**, which underwent pyran annulation with aldehyde **2.4** to afford pyran **2.5** in excellent yield as a single diastereomer. The successs of the pyran annulation led to the completion of the synthesis of dactylolide in 7.1% overall yield.

Bryostatins, which contain three highly functionized pyran rings incorporated onto a 20-membered macrolactone, are also excellent candidates to apply the pyran annulation technique. Dr. Covel demonstrated that the pyran annulation could work as a powerful tool in the approach to the core structure of the northerm hemisphere of bryostatin 1.[1] The CAA reaction between aldehyde **2.6** and stannane **2.1** provided the hydroxyallylsilane **2.7**, which underwent the first pyran annulation with aldehyde **2.2** to give the pyran product **2.8**. The TBDPS group was removed by TBAF, and the resulting primary alcohol was oxidized into an aldehyde **2.9**, which was subjected to a second pyran annulation with hydroxyallylic silane **2.3** to give the bis-pyran product **2.10**, which contains the carbon skeleton of the C3-C16 moiety of bryostatin 1 (Scheme 2.3).

This efficient and convergent route provided us a powerful approach to bryostatin analogues. Based on Wender's hypothesis, the northern hemisphere of bryostatin 1 acts as a spacer domain, presumably only assisting to help bryostatin to maintain certain conformations, and the removal of substituents on the A and B ring will not have a dramatic change on its binding affinity or biological activity. We devised our first bryostatin analogue **2.11**, which has the simplified pyran rings on the northern hemisphere, but kept all the functionality on the southern hemisphere as the recognition



Scheme 2.2 The total synthesis of dactylolide



Scheme 2.3 Synthesis of core structure of northern hemisphere of bryostatin 1

domain (Figure 2.1). The 2,6-*cis* pyran rings were to be constructed by the pyran annulation. The exocyclic olefins on the A and B rings would allow us to install different groups there and study the structure activity relationship of the northern hemisphere.

Dr. Truong and Dr. Sanchez in our group accomplished the synthesis of the first bryostatin analogue **2.11**.[3,4] The retrosynthesis of this analogue is outlined in Figure 2.2. The target molecule was expected to be prepared from the advanced tricyclic intermediate **2.12**, which was disconnected on the A ring into aldehyde **2.13** and hydroxyallylsilane **2.14**. Those two fragments were to be coupled by a pyran annulation. The formation of the B ring was also expected to come from another pyran annulation between aldehyde **2.15** and allylsilane **2.3**. Both allylsilane **2.14** and **2.3** would be prepared from reactions using the substituted stannane **2.1**. The aldehyde **2.15** was to be planned to be prepared from the acyclic thioester, which would go through a cyclization and dehydration in the presence of acid to form the C ring glycal. The linear thioester

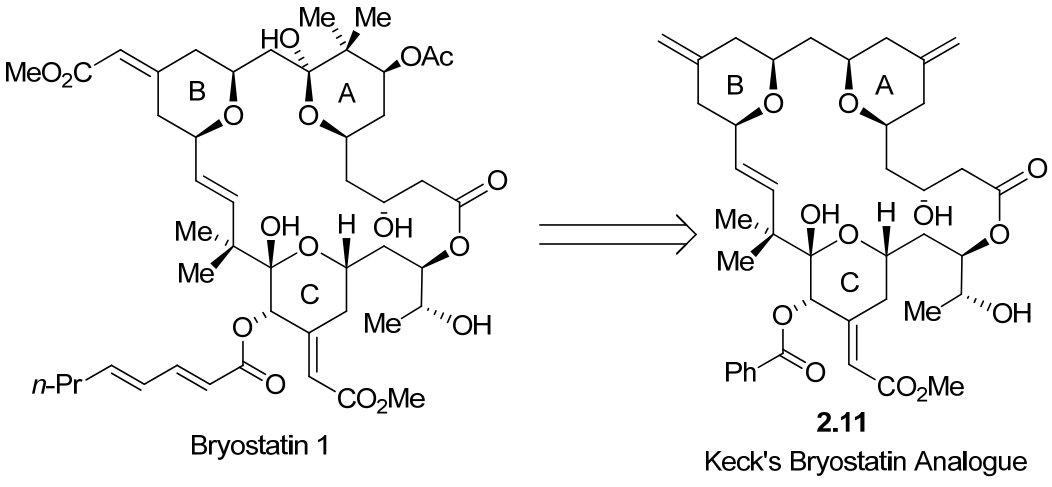


Figure 2.1 Keck's bryostatin analogue

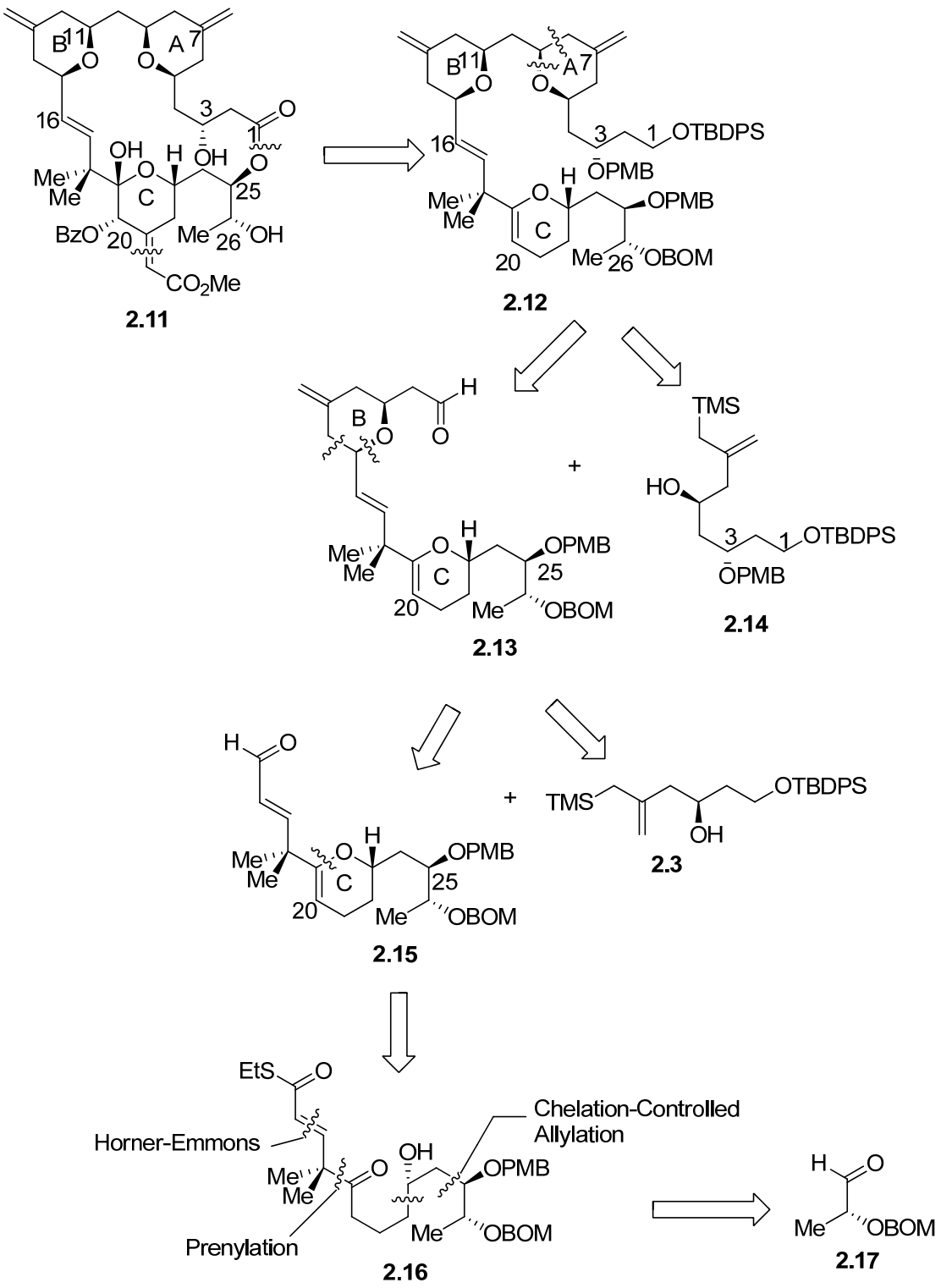
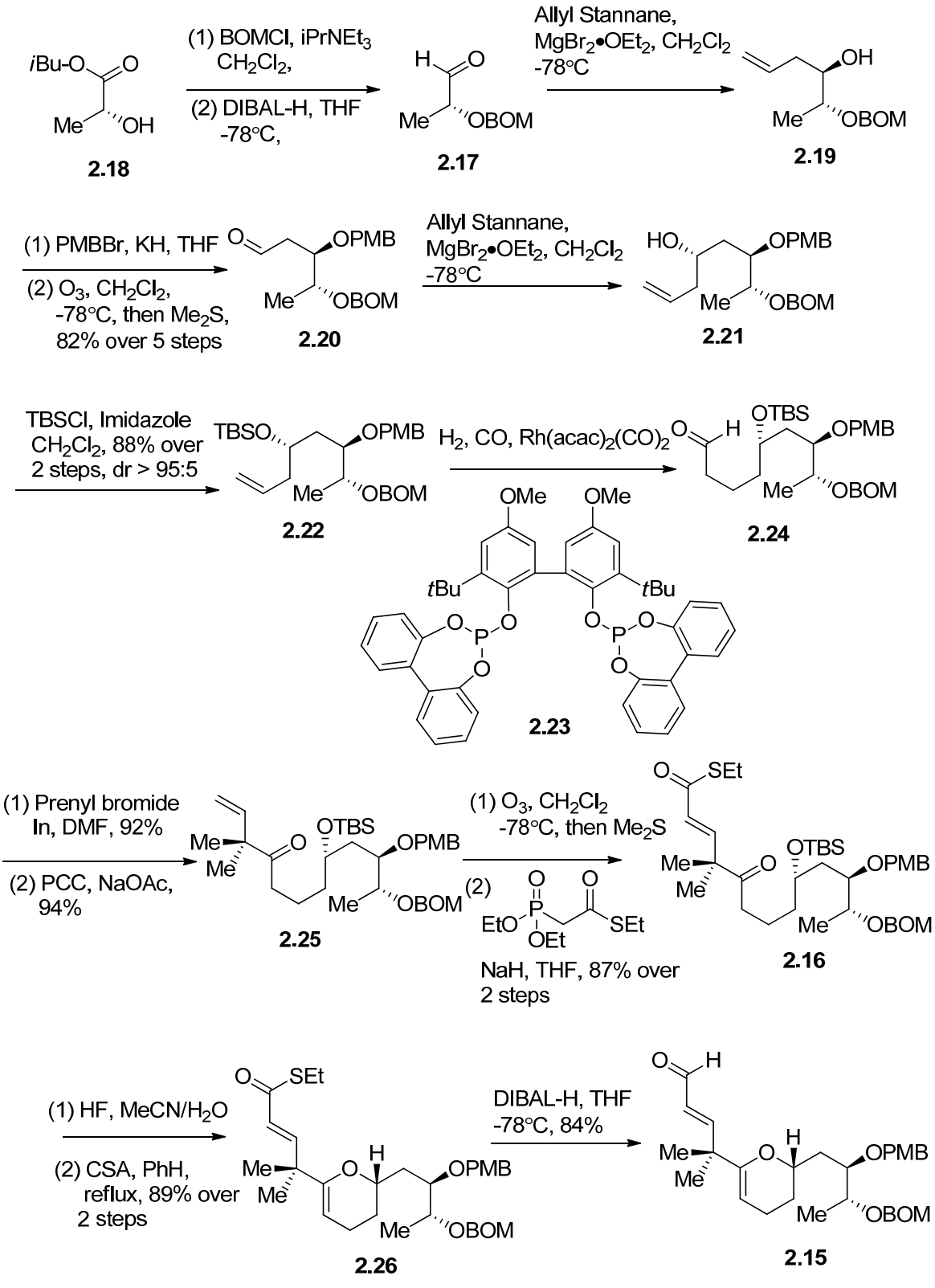


Figure 2.2 Retrosynthesis of Keck's bryostatin analogue

2.16 would be prepared from the simple aldehyde **2.17** through a series of carbon-chain elongation reactions, which include Horner-Emmons reaction, prenylation, and substrate controlled allylation.

The synthesis of aldehyde **2.15** started with commercially available (*R*)-isobutyl lactate **2.18** (Scheme 2.4). BOM protection and half reduction by DIBAL-H afforded the aldehyde **2.17**. Chelation-controlled allylation by reaction with allylstannane and $MgBr_2 \cdot Et_2O$ provided the homoallylic alcohol **2.19** as a single diastereomer. After protection of the resulting alcohol as a PMB ether, oxidative cleavage of the olefin using ozonolysis led to aldehyde **2.20**. The BOM and PMB ethers served both as protecting groups and also as directing groups to set the stereocenters on the C25 and C23 positions. Another chelation-controlled allylation was utilized to set a new stereocenter at C23. The resulting alcohol **2.21** was then protected as a TBS ether to give olefin **2.22**. The Buchwald protocol of hydroformation with a bulky ligand **2.23** smoothly delivered the desired terminal aldehyde **2.24** in excellent yield. Treatment of aldehyde **2.24** with a prenyl indium reagent generated in situ in DMF afforded a mixture of alcohols, which were then oxidized with a combination of PCC and NaOAc to afford ketone **2.25**. The olefin on **2.25** was oxidatively cleaved by ozonolysis. The resulting aldehyde is not stable, and was immediately subjected to a Horner-Emmons reaction to give the desired α, β-unsaturated thiol ester **2.16.** Deprotection of the TBS ether using HF/py buffer, and the ensuing cyclization and dehydration promoted by CSA in benzene gave the desired glycal **2.26** in one pot. Half-reduction of the thiol ester with diisobutylaluminium hydride at -78 °C provided the desired α,β-unsaturated aldehyde **2.15** without formation of the fully reduced product.

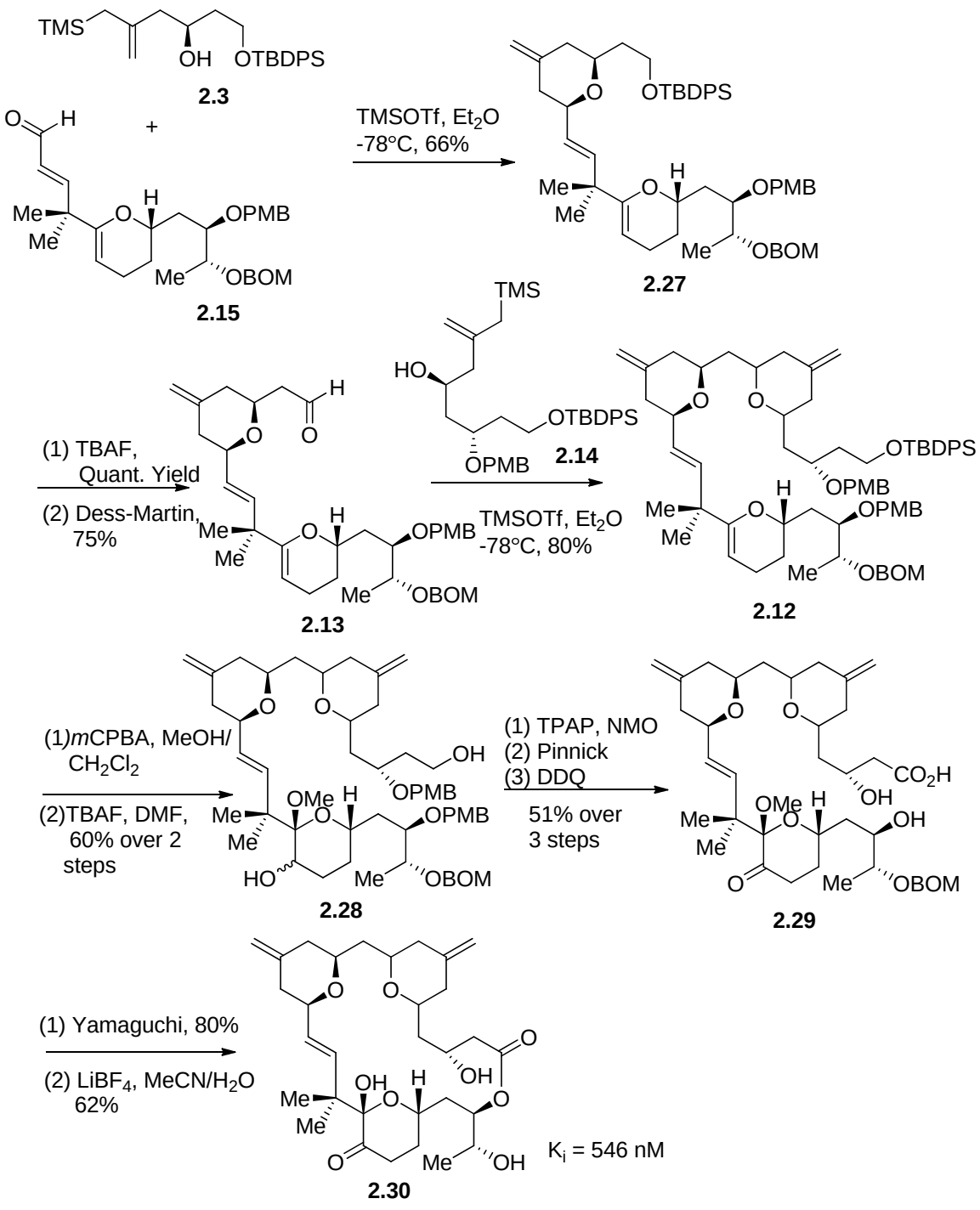


Scheme 2.4 The synthesis of southern hemisphere of Keck's first analogue

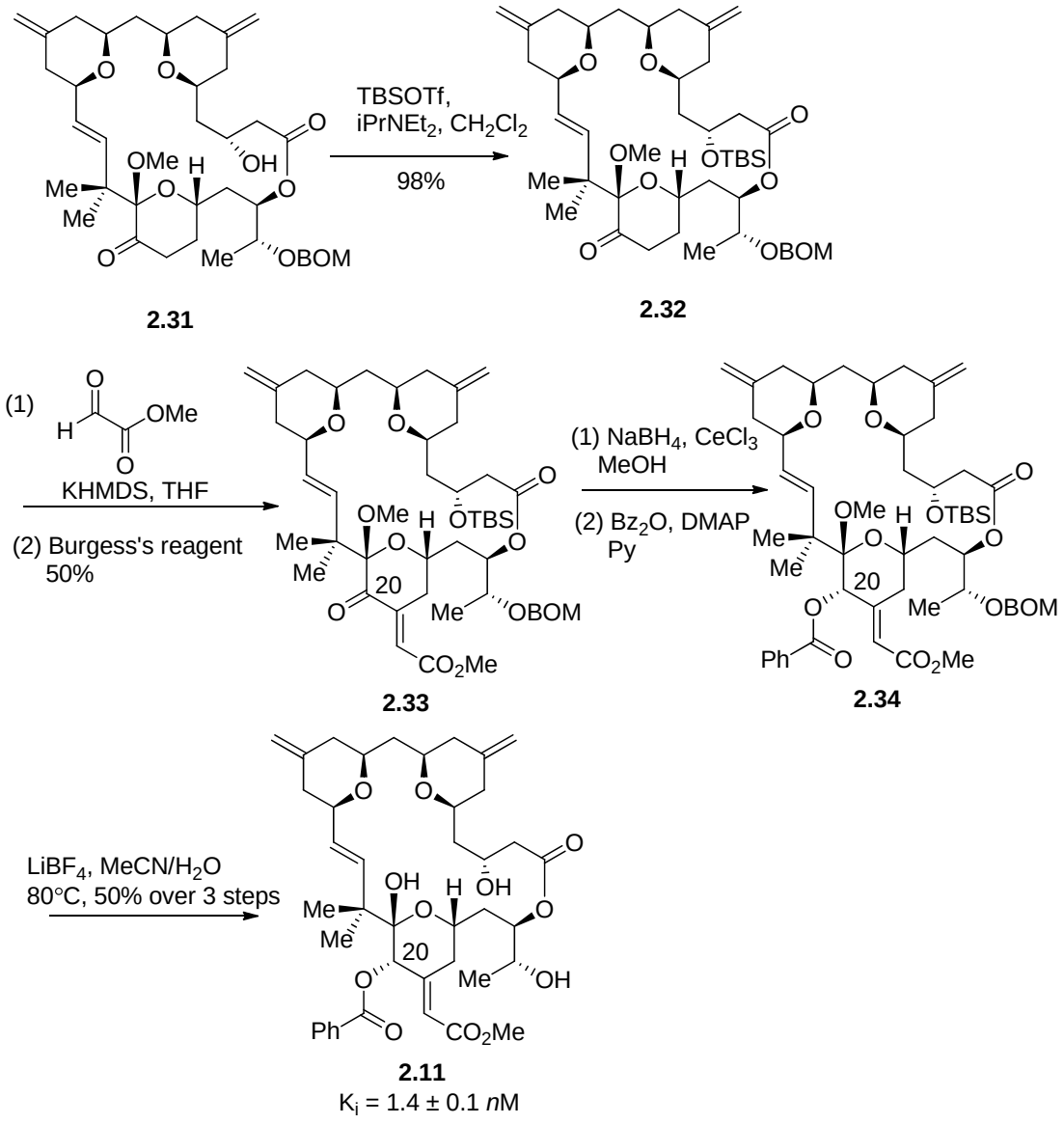
The pyran annulation between the aldehyde **2.15** and allylsilane **2.3** led to pyarn product **2.27** (Scheme 2.5). The removal of the TBDPS group and exposure to Dess-Martin oxidation conditions afforded aldehyde **2.13**.[5] A second pyran annulation with allylsilane **2.14** furnished the tricyclic product **2.12**. The glycal moiety on **2.12** was oxidized with *m*CPBA in MeOH, and the resulting epoxide was not stable, resulting in in situ methanolysis to afford the ketal. Removal of the TBDPS ether at C1 was achieved with TBAF, and the resulting diol **2.28** was oxidized to keto-aldehyde by TPAP and NMO. Pinnick oxidation transformed the aldehyde into an acid, and the deprotection of the PMB group afforded the seco-acid **2.29**. Yamaguchi macrolactonizaiton was used to cyclize the macrocycle and global deprotection with $LiBF_4$ finished the analogue **2.30** with a tricyclic skeleton similar to bryostatin 1.[6,7]

Analogue **2.30** was tested by our coworker, Dr. Blumberg at the NIH for its binding affinity with PKCα, the results shows the analogue has a K_i = 546 *n*M, which is about 2 orders of magnitude lower than bryostatin 1 (K_i = 1.37 ± 0.17 *n*M). The biological results suggest that functional groups on the C ring are important in binding.

Dr. Sanchez synthesized analogue **2.11** with full functionality on the C ring from Dr. Troung's work (Scheme 2.6). The synthesis started with advanced intermediate **2.31**. The C3 hydroxyl group was protected as a TBS ether. The C20 ketone on **2.32** was subjected to an aldol reaction with methyl glyoxylate and an elimination reaction promoted by Burgess's reagent was used to afford the enoate **2.33**. The ketone on C20 was reduced with Luche conditions,[8] and the resulting alcohol was immediately esterified with benzoic anhydride to generate the ester **2.34**. The global deprotection with $LiBF_4$ smoothly delivered the final product **2.11**. The biological test result from Dr. Blumberg



Scheme 2.5 Troung's Synthesis Tricyclic Bryostatin Analogue



Scheme 2.6 The completion of bryostatin analogue

indicated **2.11** showed similar binding affinity with PKCα (K_i = 1.4 ± 0.1 *n*M) as does bryostatin 1 (K_i = 1.37 ± 0.17 *n*M).

Synthetic and Biological Study of Bryostatin Analogue With C7 Acetate

After the completion of the first generation synthesis of bryostatin analogues, we sought to improve the synthetic route and explore to the bioactivities of diversified analogues. The second generation synthesis of bryostatin analogues concentrated on the follow aspects: (1) the first generation synthesis proceeded in a linear manner, through which the pyran rings were constructed sequentially. The linear route made it difficult to bring up enough material for biological testing. Only 0.6 mg of **2.11** was prepared. A more convergent route would make the synthesis more efficient and address the problem of supply; (2) the acid-sensitive glycal **2.15** decomposed during the pyran annulation resulting in a modest yield; (3) the structure and activity relationship study required us to install different functionality. Besides the analogue **2.11**, we were also interesting in the preparation of analogues with different functional groups on C7 and C20 positions.

The revised route to bryostatin analogues is outlined in Figure 2.3. The bryostatin analogues **2.35** was expected to be prepared from intermediate **2.36**, which was disconnected into aldehyde **2.37** and allylsilane **2.38**. The pryan annulation would act to connect two equally complicated moieties, with concommitment formation of the B ring, which represents a new route compared to the bryostatins. We envisioned that the allylsilane **2.38** would be prepared from the ester **2.39**, which would be constructed using another pyran annulation between aldehyde **2.40** and allylsilane **2.41**. Aldehyde **2.40** was

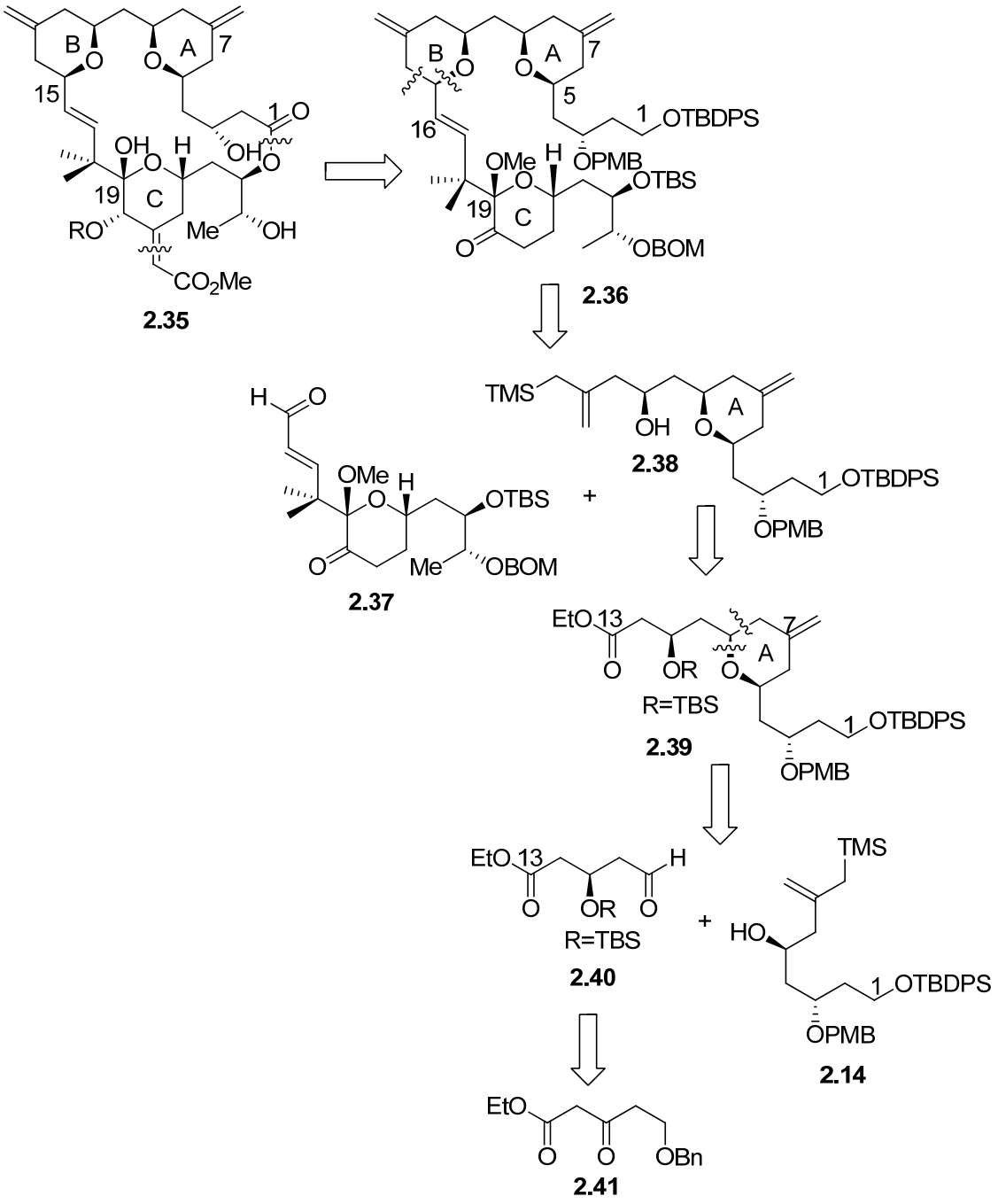
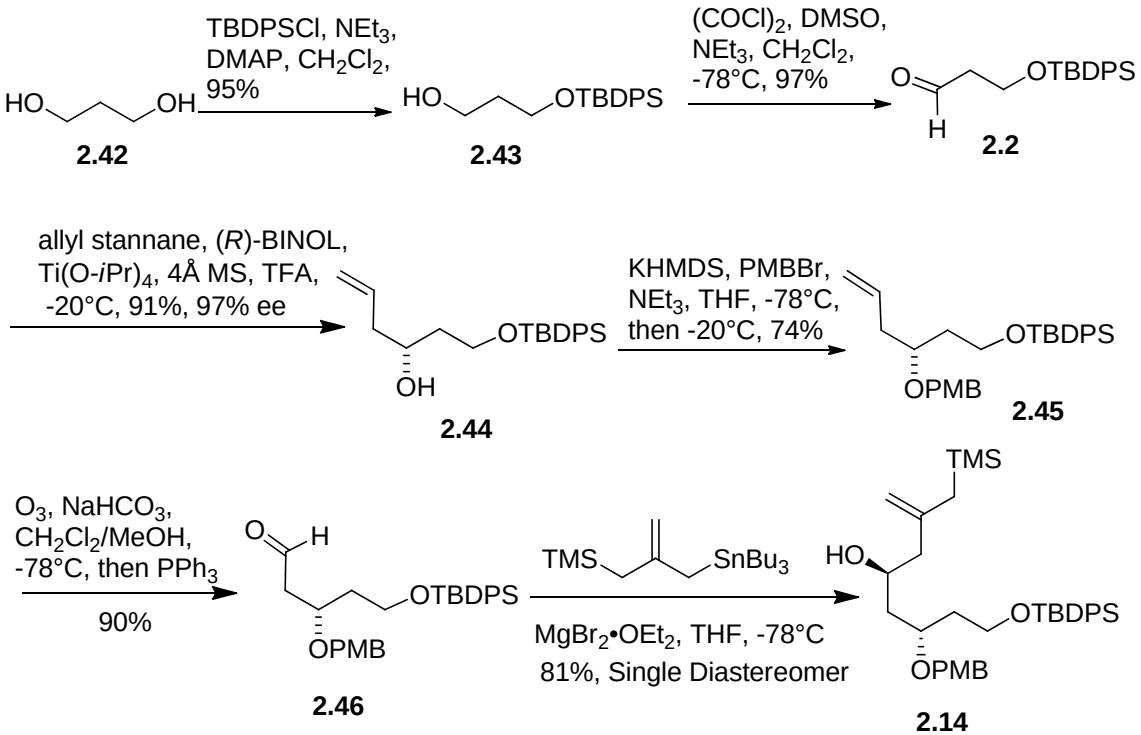


Figure 2.3 Retrosynthesis of the second generation route to bryostatin analogues

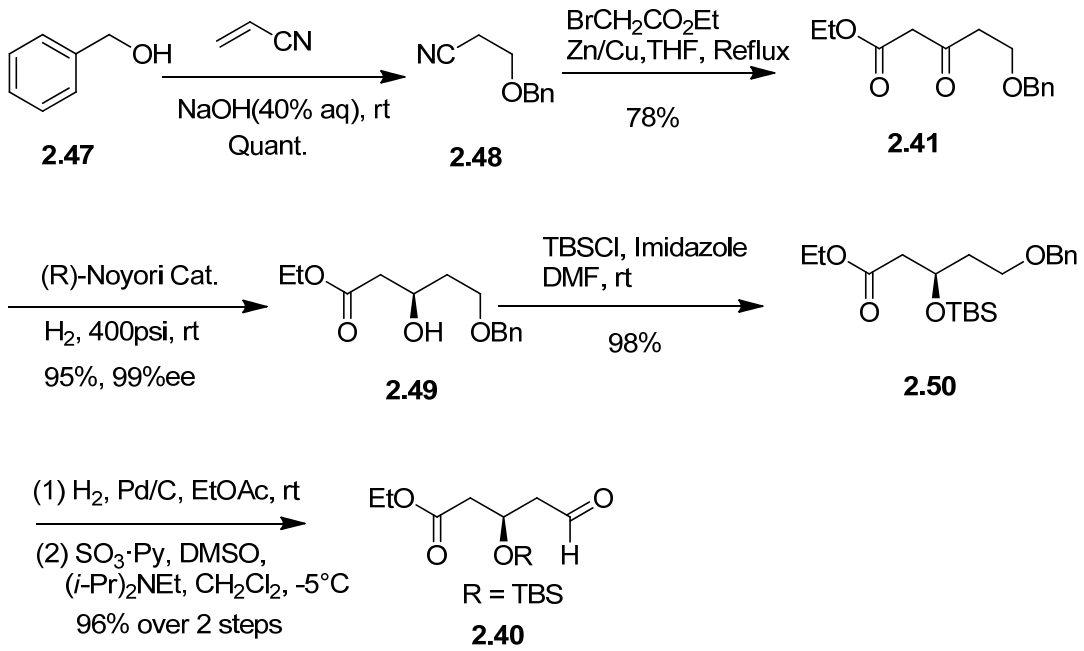
expected to be synthesized from β-keto ester **2.41** by Noyori asymmetric hydrogenation.

The synthesis of silane **2.14** began with monoprotection of 1,3 propandiol **2.42** with a TBDPS group (Scheme 2.7) to give the alcohol **2.43**, which was oxidized by Swern oxidation to afford aldehyde **2.2.** Catalytic asymmetric allylation of aldehyde **2.2** provided the homoallylic alcohol **2.44** with excellent yield and high enantioselectivity.[9] KHMDS was used at low temperature to install the PMB protecting group on **2.44** smoothly without observation of silyl group transfer. The use of PMB imidate was also tested to install the PMB ether on C3 position; however, the difficulty of isolation after work-up makes the first method superior. The resulting olefin **2.45** was cleaved by ozonolysis to give aldehyde **2.46**. A chelation-controlled allylation converted aldehyde **2.46** into β-hydroxyallylsilane **2.14** as a single diastereomer using $MgBr_2 \cdot OEt_2$ as the chelating reagent.[10]



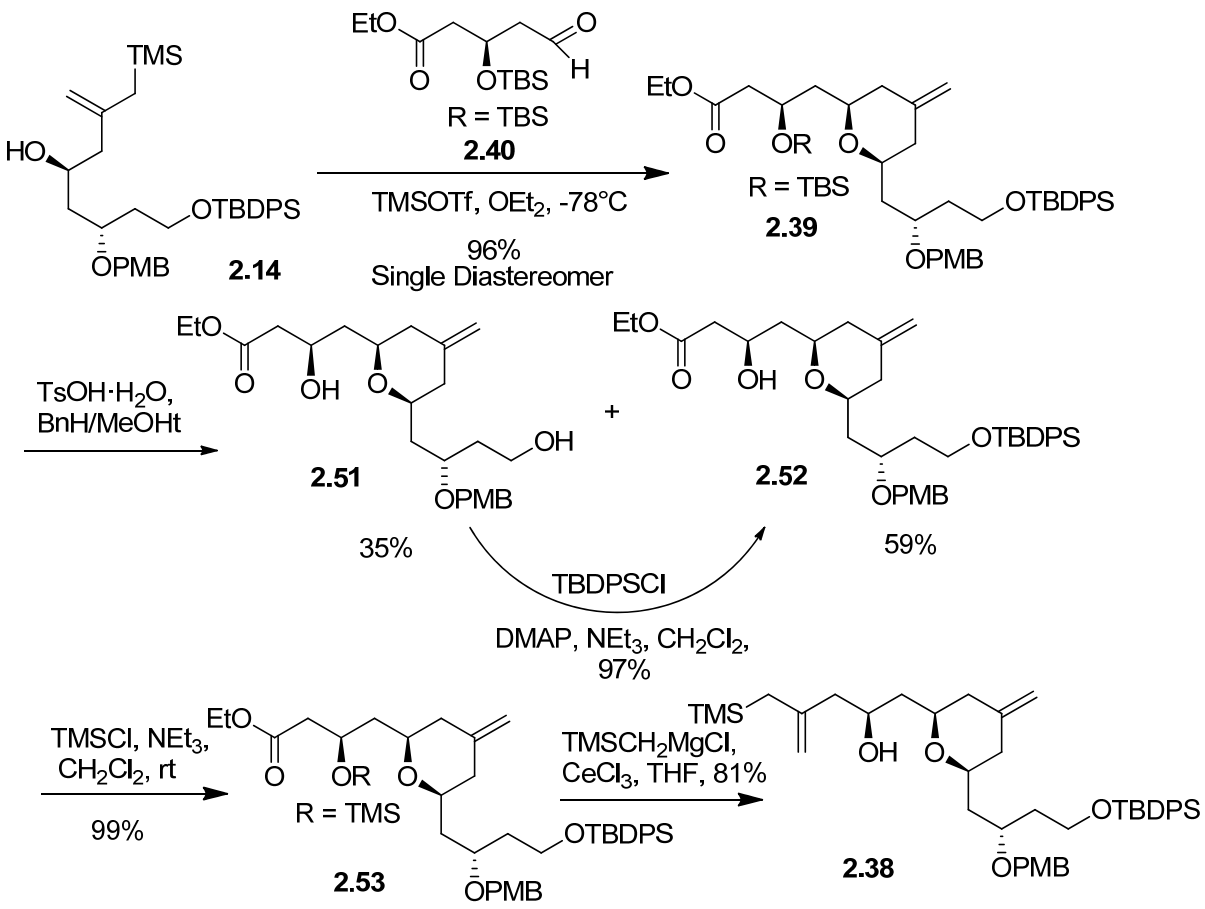
Scheme 2.7 Synthesis of intermediate allylsilane **2.14**

The synthesis of aldehyde **2.40** started from benzyl alcohol **2.47** (Scheme 2.8). Michael addition between benzyl alcohol **2.47** and acrylonitrile in the presence of 40% NaOH aqueous solution gave nitrile **2.48** in quantitative yield without any purification after workup. Reformatsky reaction of α-bromo acetate with nitrile **2.48** and Zn/Cu couple gave a volatile enamine, and the following hydrolysis converted the enamine into *β*-keto ester **2.41**.[11] Slow adding α-bromo acetate into the reaction via syring pump proved to be the key for the Reformatsky reaction. The Noyori asymmetric hydrogenation was utilized to reduce **2.41** into alcohol **2.49** with high yield and high enantioselectivity.[12] This procedure was utilized to prepare 50 grams of product **2.49** without any problem in scale up. The hydroxyl group on alcohol **2.48** was protected with a TBS group to give silyl ether **2.50**. Deprotection of the benzyl group by catalytic hydrogenation over Pd/C, and Parikh-Doering oxidation afforded the aldehyde **2.40**.



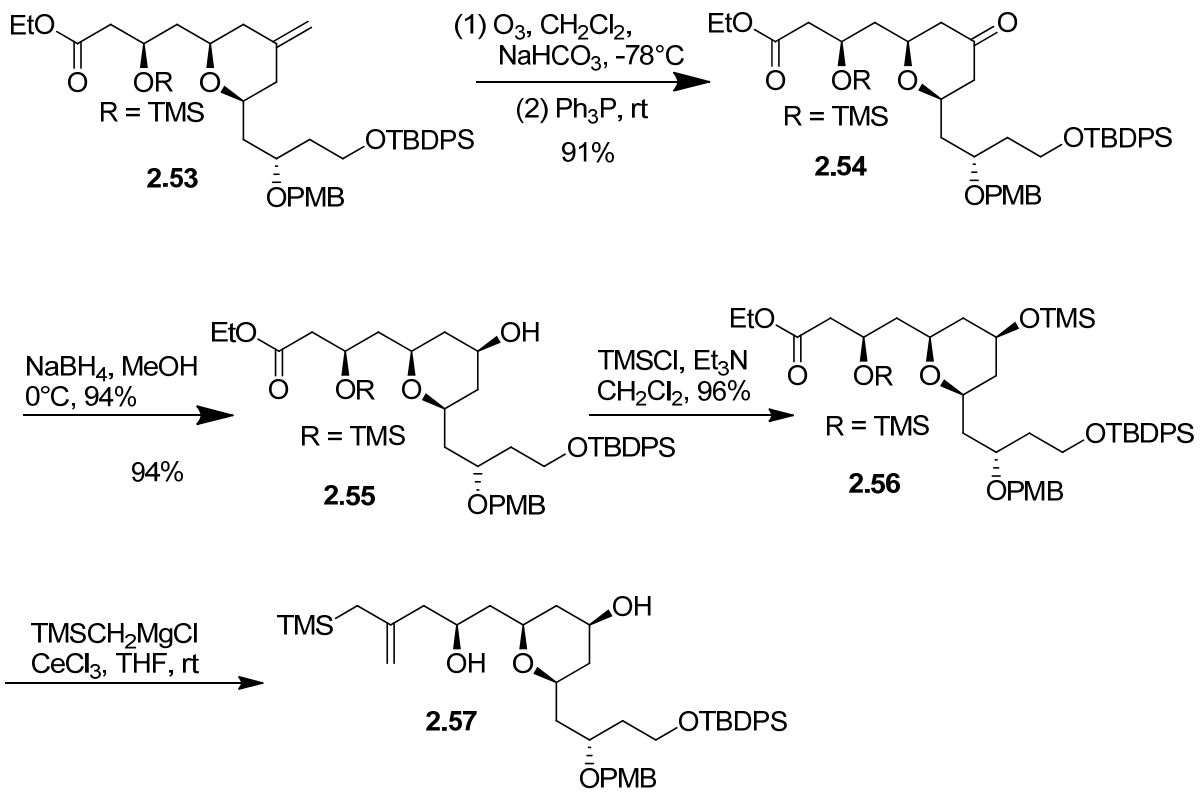
Scheme 2.8 Synthesis of aldehyde **2.40**

With hydroxyallylsilane **2.14** and aldehyde **2.40** in hand, we were able to couple those two pieces using the pyran annulation (Scheme 2.9). In the presence of the Lewis acid TMSOTf, the pyran annulation gave the pyran **2.39** smoothly with a yield of 96% as a single diastereomer. The selective deprotection of the TBS group on **2.39** was not straightforward. A few reaction conditions with different acids and solvents were screened and the products after deprotection always included some amount of **2.51** with loss of both TBS and TBDPS groups. We also tested the route by replacing the TBS group with TES on aldehyde **2.40** in order to differentiate the deprotection of TES and TBDPS groups after pyran annulation; however the pyran annulation between the aldehyde with TES and hydroxyallylsilane **2.14** proceeded in low yield, and the TES group came off during the pyran annulation. The optimized reaction conditions for deprotection of the TBS group proved to be treatment of **2.39** with 2.0 equivalents of *p*-toluenesulfonic acid in the media of benzene/MeOH (60/40) for 5 h at rt. After column chromatography, the product **2.51** was isolated in 35% yield and the desired product **2.52** with 59% yield. Fortunately, the product **2.51** could be easily converted to **2.52** by treatment with TBDPSCl, NEt_3 and 4-dimethylaminopyridine in a yield of 97%, which gave a total yield of 92% from **2.39** to **2.52**. The hydroxyl group on **2.52** was protected with a TMS to give **2.53** in almost quantitative yield. Subjecting this ester to the Bunnelle reaction conditions afforded the hydroxylallylsilane **2.38** in 81% yield after acidic work-up. Dehydration of $CeCl_3 \bullet 7H_2O$ was critical to the Bunnelle reaction. Trace amounts of water would dramatically decrease the yield. In order to prepare anhydrous $CeCl_3 \bullet 7H_2O$, the finely ground crystals were stirred at 160 °C under vacuum of 1 mm Hg for 16 h.



Scheme 2.9 Synthesis of hydroxyallylsilane **2.38**

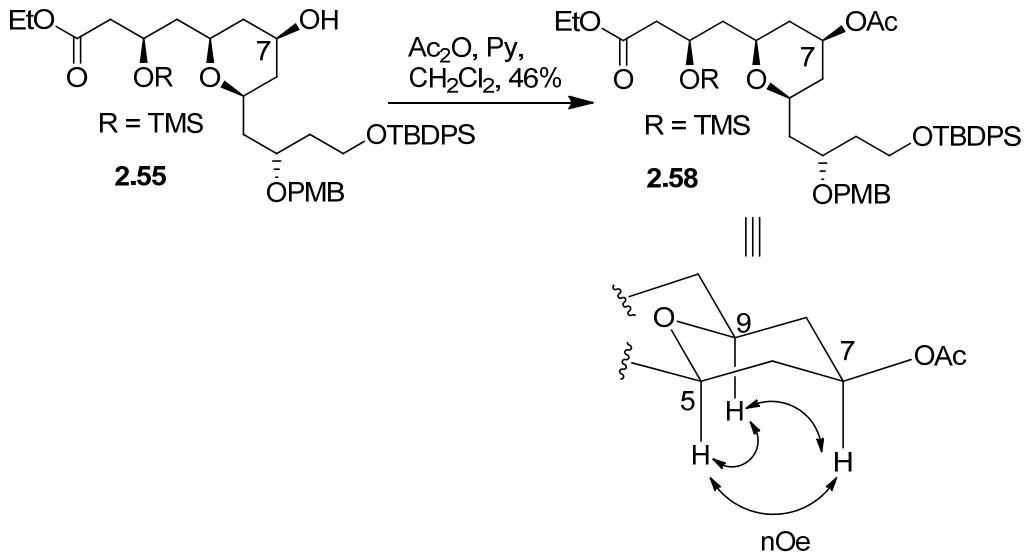
In order to diversify the functionality at the C7 position, we investigated routes to modify the functionality on C7 (Scheme 2.10). The olefin in pyran **2.53** was cleaved by ozonolysis and reduced by PPh_3 to give ketone **2.54**, which was reduced to alcohol **2.55** by $NaBH_4$. The free hydroxyl group in **2.55** was protected with a TMS group to afford the precursor **2.56**. The Bunnelle reaction was utilized again to convert **2.56** to hydroxyallylsilane **2.57**. The free hydroxyl group on the C7 position of the hydroxyallylsilaneprovides us an opportunity to synthesize bryostatin analogues with different functionalities on the C7 position.



Scheme 2.10 Synthesis of allylsilane **2.57**

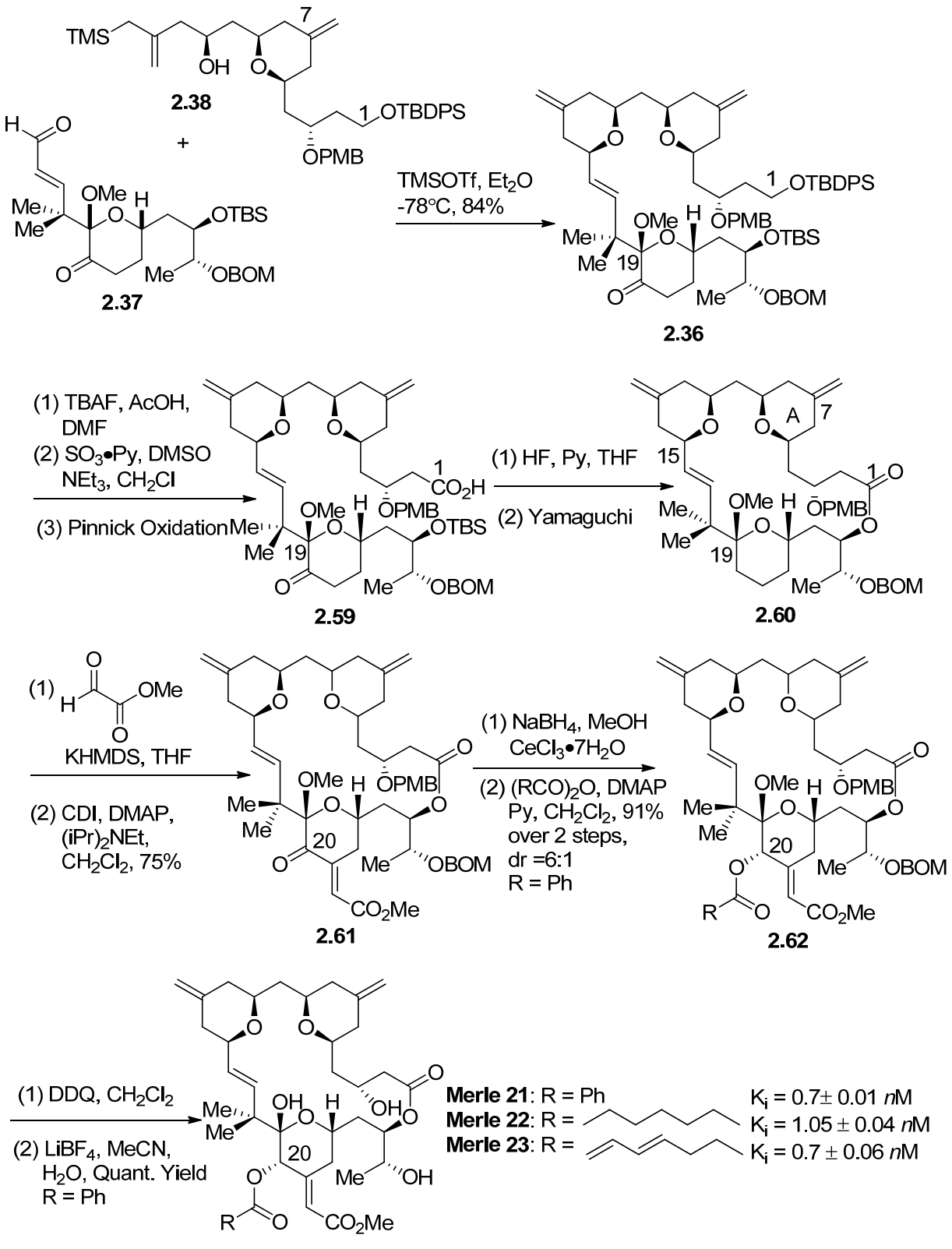
The stereochemistry at the C7 position was confirmed by observation of nOe of the C7 acetate product **2.58** from alcohol **2.55**. The nOe results indicated that the proton on the C7 was axial (Scheme 2.11).

While this work was in progress, Dr. Kraft in our group prepared aldehyde **2.37**.[13] With both allylsilane and aldehyde in hand, we were able to test the pyran annulation. The coupling between hydroxyl aldehyde **2.37** and allylsilane **2.38** afforded the tricylic product **2.36** in good yield and as a single diastereomer. Dr. Kraft successfully carried this tricyclic product to the final bryostatin analogues, Merle 21-23, with different groups on the C20 position (Scheme 2.12).



Scheme 2.11 Confirmation of stereochemistry of C7 hydroxyl group

The TBDPS group on C1 of the resulting pyran annulation product **2.36** was selectively removed by treatment with TBAF and AcOH without removing the TBS group on C25. The free alcohol was exposed to Parikh-Doering oxidation followed by Pinnick oxidation of the crude aldehyde to give the carboxylic acid **2.59** in excellent yield. The deprotection of the TBS group with HF/py afforded the seco acid, which was cyclized to give macrolactone **2.60** by utilizing Yamaguchi conditions. The remaining steps to the final products required functionalizing the C-ring and global deprotection. During the aldol reaction between ketone **2.59** and freshly prepared glyoxylate, the deprotonation of α-H of C20 ketone with KHMDS also induced elimination at the C3 position due to the electron withdrawing effect from the C1 carbonyl. After optimiziation of the reaction conditions, the use of 3 equiv of freshly prepared LDA solution could avoid the undesired elimination reaction, affording the desired aldol product in 76% yield with 19% of recovered starting material. The ensuing elimination of the aldol product



Scheme 2.12 Kraft's completion of bryostatin analogues, Merle 21-23

turned into a real challenge. Conditions used in previous syntheses of bryostatins led to low yields or complete decomposition. Ultimately, a new procedure for this very demanding reaction was devised, which involved treatment with carbonyl diimidazole (CDI) in the presence of $(i\text{-Pr})_2$NEt to give the enoate **2.61**. Luche reduction of the C20 ketone in **2.61** gave the desired alcohol, which was immediately acylated to give protected versions of analogue precursors **2.62**. Removal of the protecting groups commenced by deprotection of the PMB group with DDQ. Finally, global deprotection of the remaining groups could be accomplished using the $LiBF_4$ conditions to afford analogues Merle 21-23.[13]

The analogues were submitted to Dr. Blumberg at the National Cancer Institute for biological tests. All three of these compounds proved to have similar or higher binding affinity for PKCα than does bryostatin (bryostatin 1, K_i = 1.35 *n*M) since all the analogues have the same recognition domain as bryostatin 1.[14] The different substituted groups on the C20 position have little effects on binding affinity with PKC, which provides a tunable position for future analogue design. Our attention was more focused on whether the analogues behaved like bryostatin 1 in living cells. Each of these analogues was screened for activity on the proliferation and attachment of U937 leukemia cells.[15] In these assays, phorbol esters inhibit proliferation and induce attachment. Bryostatin 1 shows only a limited effect and correspondingly blocks the effect of the phorbol ester at high concentration. If the analogues were to act simply as PKC activators, they would inhibit proliferation and induce attachment both alone and in the presence of PMA. If they were to act as functional antagonists, they would show little reduction in proliferation or induction of attachment and would restore proliferation and block

attachment in the presence of 10 nM PMA. The biological test results indicated that all three analogues behaved like PMA instead of bryostatin. Results with Merle 23 in the proliferation and attachment assay of U937 cell line are shown in Figure 2.4 and 2.5. It is clear that the fingerprint displayed here by Merle 23 is virtually identical to that of the tumor-promoting phorbol ester PMA and distinctly different from that of bryostatin 1. According to Wender's hypothesis, the northern hemisphere acts only as the spacer domain, but the biological tests of Merle 21-23 suggest that this spacer domain also has a contribution to the unique bioactivities of bryostatin 1. This may have significant implications regarding the projected use of such compounds as therapeutic agents.

Merle 23 can be seen to differ from bryostatin 1 at just four positions in the northern hemisphere. The identification, through synthesis, of the contribution of substituents in this region to the bryostatin-like behavior became essential to our study. We planned to investigate each functional group through chemical synthesis, and selected as our next target was analogue with the C7 acetate on the A ring.

Wender's docking study indicated that the C7 functionality of bryostatin is proximate to a conserved tryptophan residue in the novel class of PKC isozymes and a conserved tyrosine residue in the conventional class of PKC isoforms.[16] The docking studies, using the crystal structures of PKC and bryostatin 1, are guided by their pharmacophore hypotheses rather than a global conformational search. In this approach, the conformation of bryostatin 1 obtained by X-ray crystallography was overlaid with the phorbol 13-acetate found in the PKCδ C1B domain crystal. The C1 carbonyl, the C19 hydroxyl, and the C26 hydroxyl of bryostatin 1 were superimposed upon the C4, C9, and

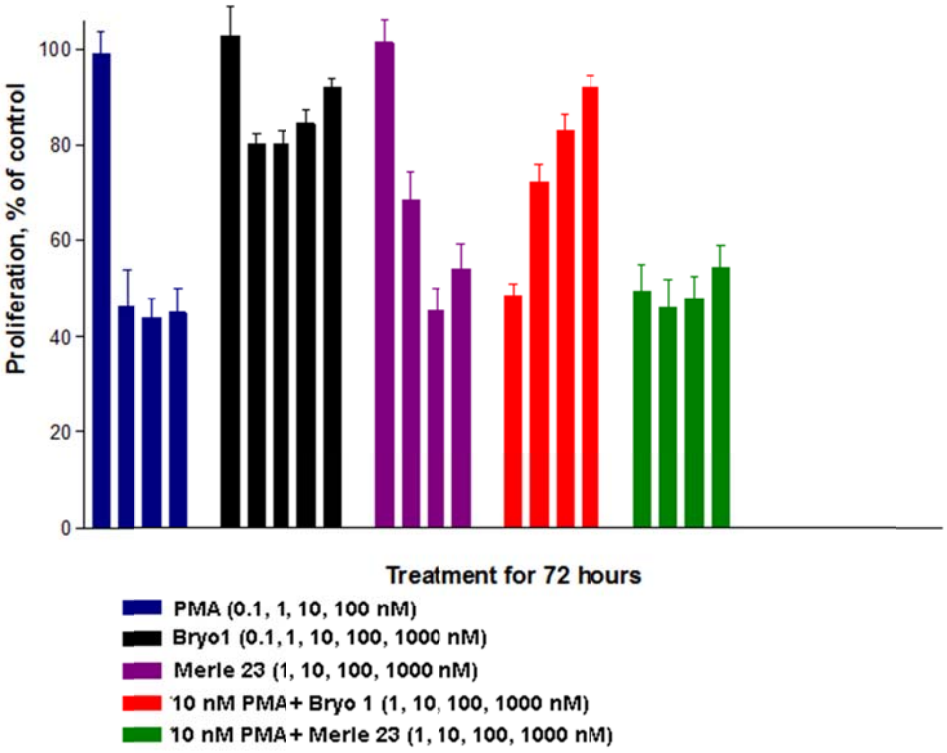


Figure 2.4 U937 proliferation assay with Merle 23

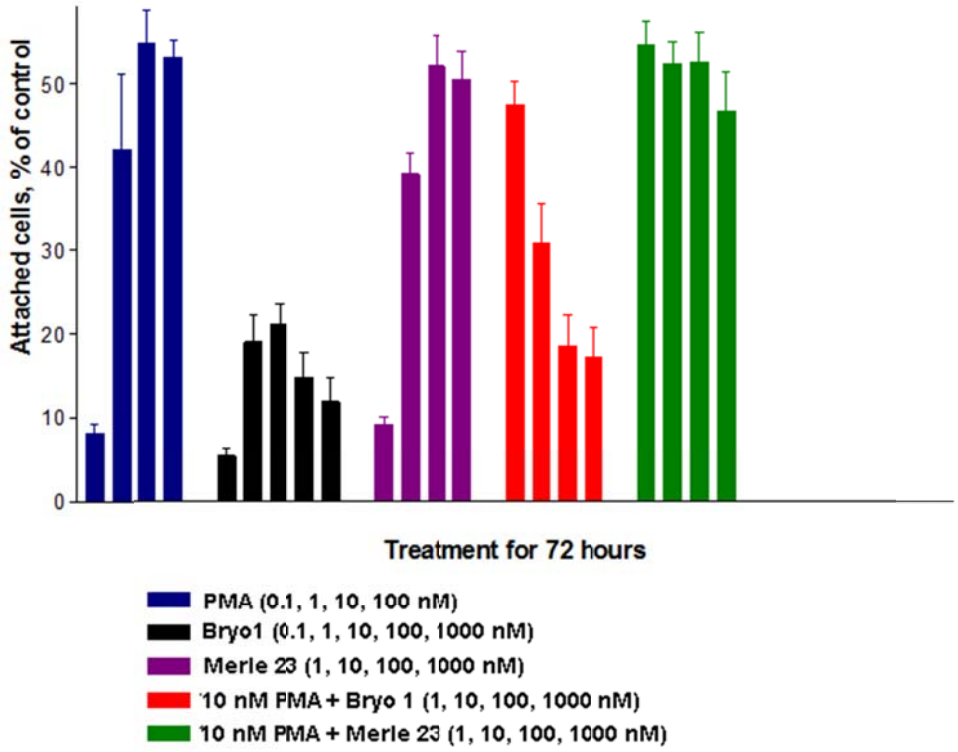


Figure 2.5 U937 attachment assay with Merle 23

C20 hydroxyls of phorbol 13-acetate. The phorbol molecule was then removed and the resulting bryostatin–PKCδ-C1B complex was minimized using the AMBER force field.

We expected that the synthesis of C7 acetate analogue **2.63** would provide us the opportunity to investigate the effect of C7 acetate on the biological activity of the bryostatin analogue. The retrosynthetic strategy is outlined in Figure 2.6. In order to avoid the problematic elimination of the PMB ether on the C3 position, we decided to cyclize the macrolactone after installation of the enoate on the C ring. This analogue would be prepared from advanced intermediate **2.64**, which we planned to synthesize from ketone **2.65**. The pyran annulation between aldehyde **2.37** and hydroxyallylsilane **2.57** was expected to allow construction of pyran product **2.65**.

Pyran annulation between C-ring enal **2.37** and allylsilane **2.57** under our standard conditions of TMSOTf in diethyl ether gave the desired tricyclic product **2.66**, as a single diasteromer, in excellent yield (Scheme 2.13). Protection of the C7 OH using TBSOTf and 2,6-lutidine gave **2.65** in almost quantitative yield. The aldol condensation with 3.0 of equiv LDA solution and methyl glyoxalate smoothly gave a diastereomeric mixture of aldol products in 92% yield, which underwent elimination by treatment with Ac_2O and 4-dimethylaminopyridine in pyridine at 60 °C to give **2.67** in 93% yield. The changes of reaction order improved the yields during the aldol and elimination steps, and avoided the possible side reactions.

The resulting enoate **2.67** was then subjected to Luche reduction followed by acylation with octanoic anhydride to give **2.64** (Table 2.1).[8] When the same conditions were applied as with Merle 21-23, a mixture of diastereomers with selectivity of only 7:1 favoring the desired product was isolated from the reaction of treatment with $CeCl_3 \cdot 7H_2O$

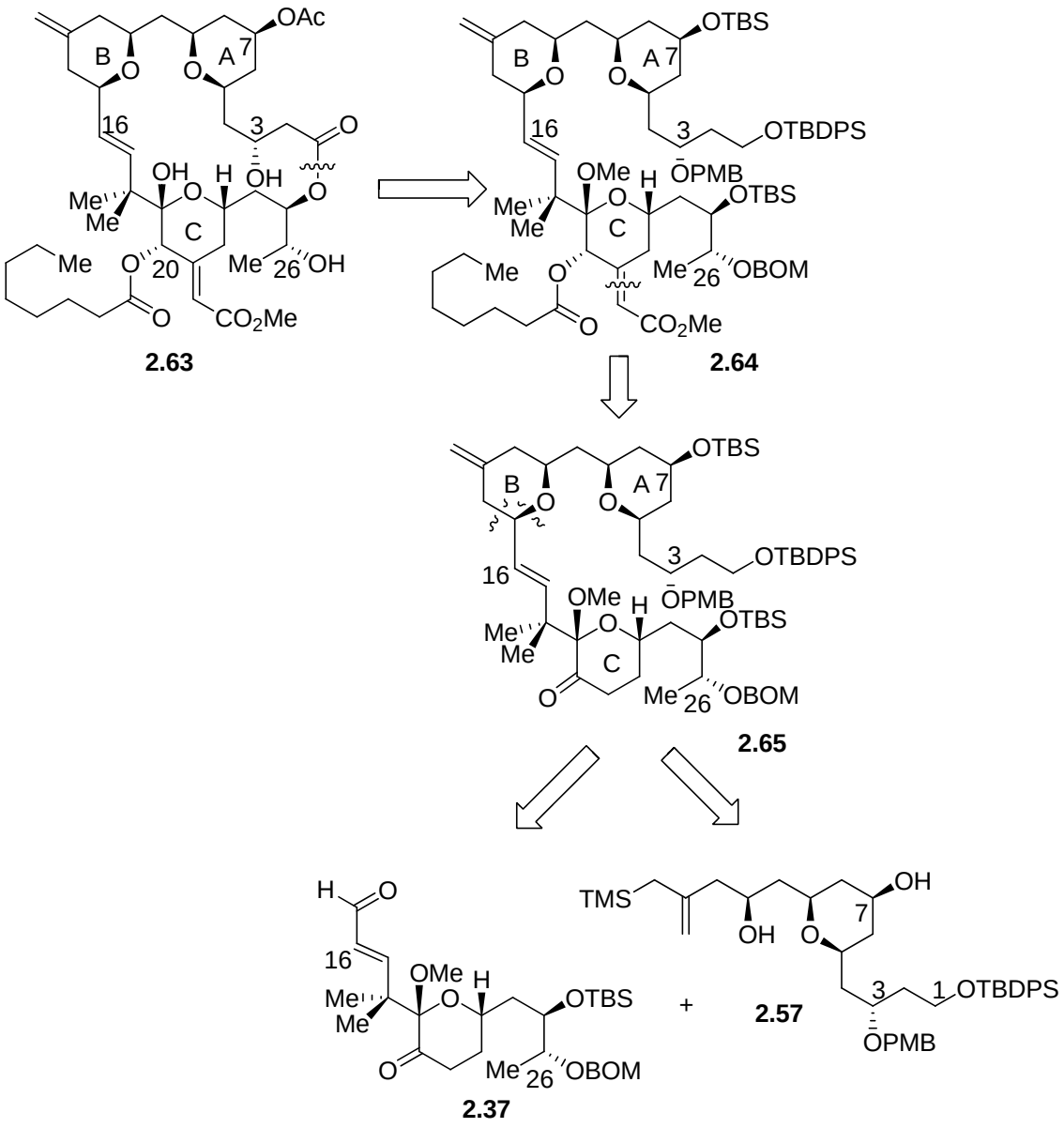
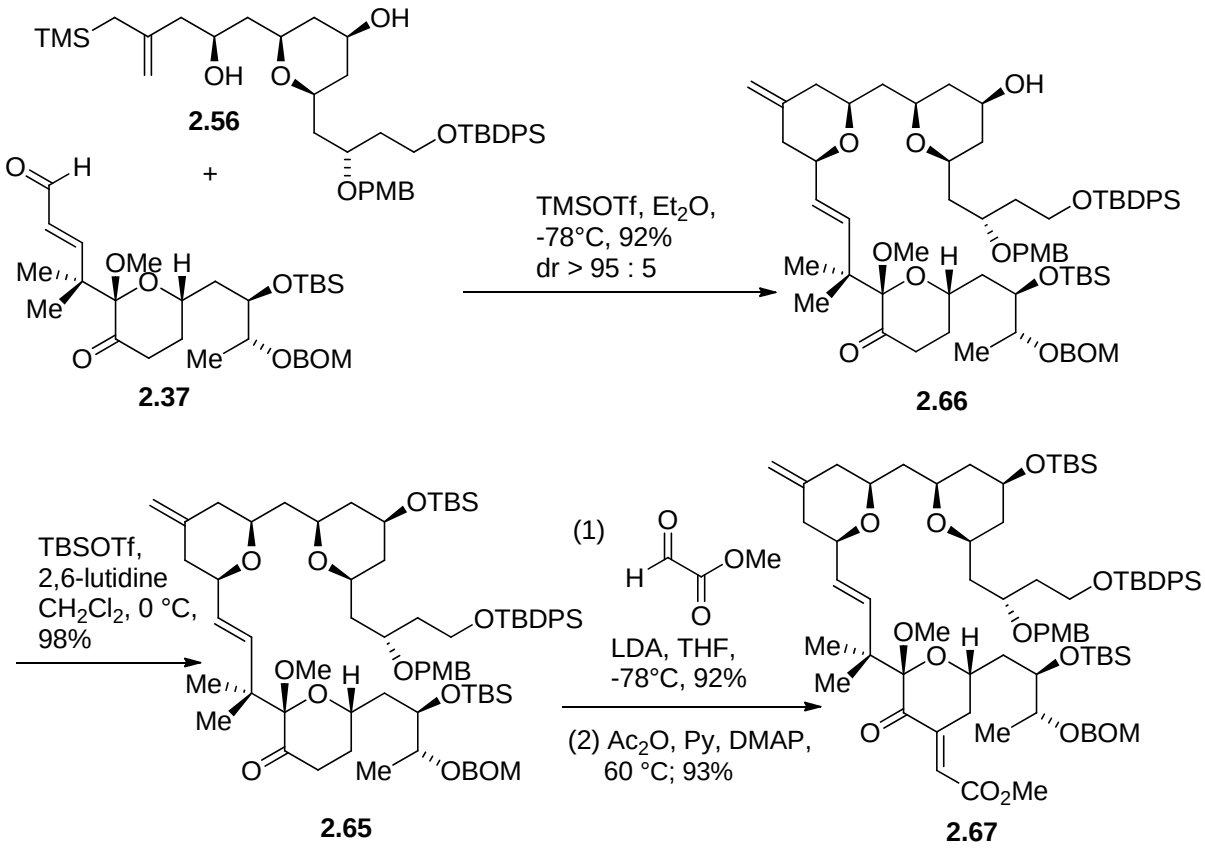


Figure 2.6 The retrosynthetic strategy to C7 acetate analogue

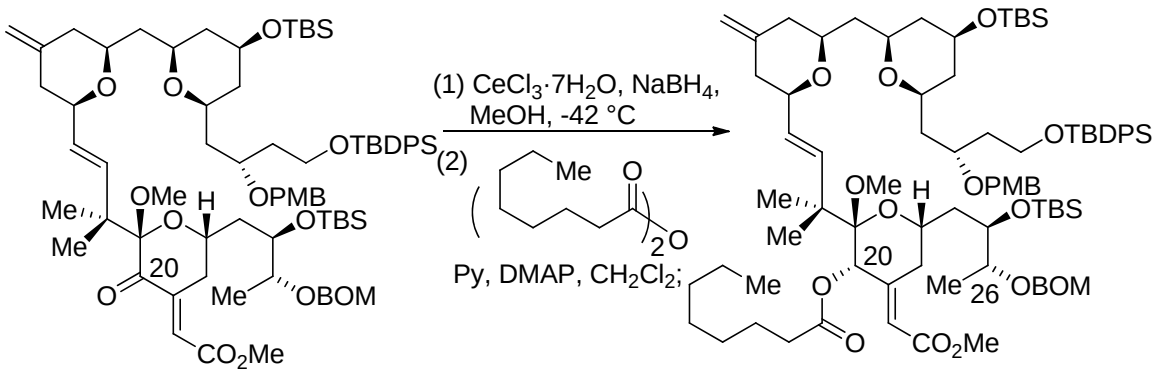


Scheme 2.13 Functionalization of C ring after pyran annulation

and $NaBH_4$ at -42 °C. Further optimization involved dissolution of $CeCl_3 \cdot 7H_2O$ at room temperature led to an improved diastereoselectivity of 22:1. The concentration also played some effect on the selectivity; the reaction in 0.005 M MeOH led to the single diastereomer of product.

Selective removal of the TBDPS group at the C1 position of intermediate **2.64** using TBAF and AcOH in DMF afforded the primary alcohol **2.68**, which was transformed to acid **2.69** by sequential Parikh-Doering and Pinnick oxidations with a quantitative yield. Removal of both TBS groups (at C7 and C25) using HF·Py then gave the corresponding dihydroxy acid **2.70**. There are examples showing the successful

Table 2.1 Luce Reduction on C20 Ketone on 2.65



2.65 **2.63**

Entry	Molarity (M)	Yield[a]	dr
1[b]	0.01	83%	7:1
2[c]	0.01	80%	22:1
3[c]	0.005	82%	>95:5

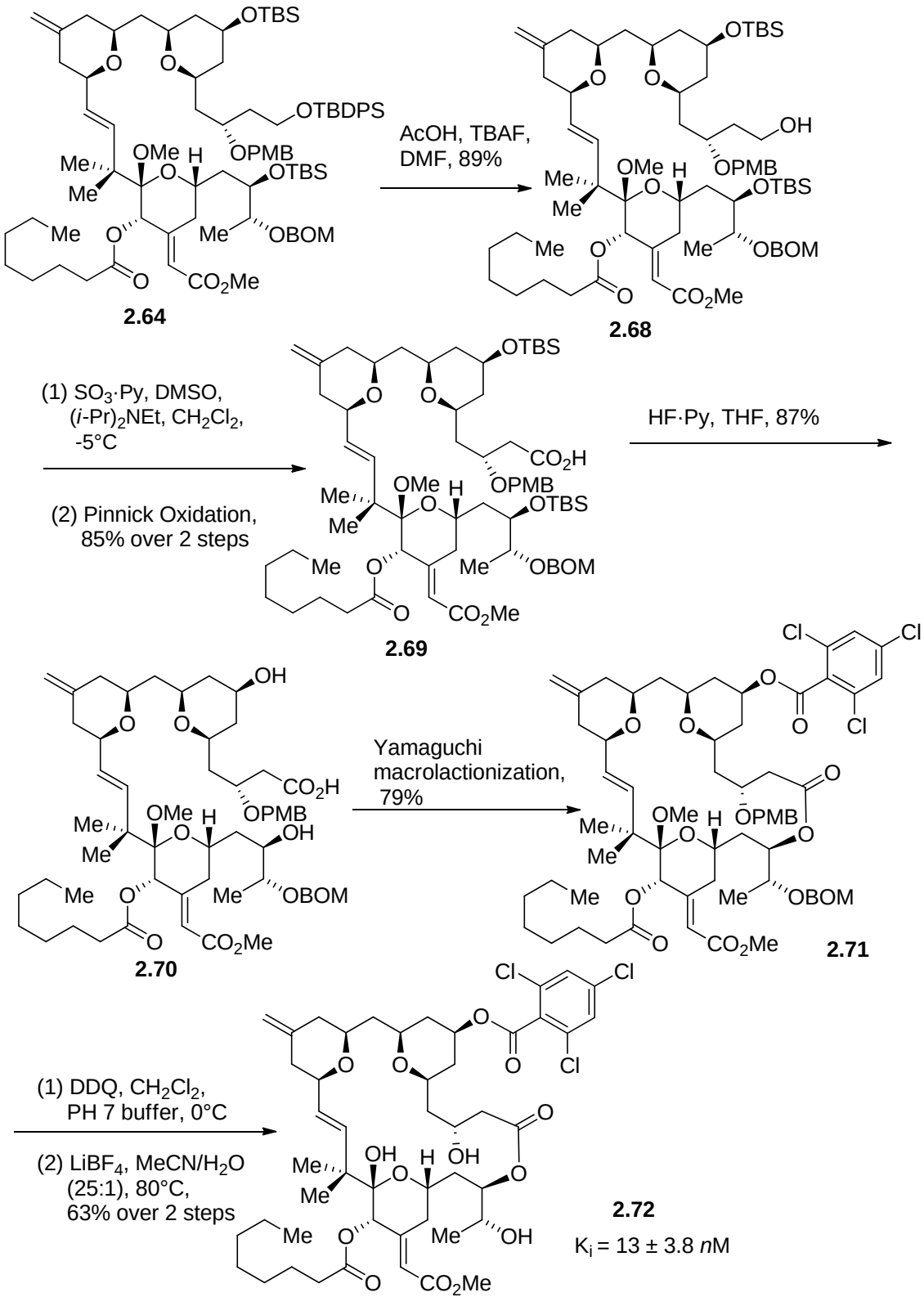
a: The yields were calculated based on the isolated ester **2.63**

b: $CeCl_3 \bullet 7H_2O$ was added at -42 °C

c: $CeCl_3 \bullet 7H_2O$ was added at rt.

regioselective macrolactonization accomplished on the dihydroxy acid substrates in the syntheses of bryostatin and analogues.[4,17] When we applied the Yamaguchi reaction to the dihydroxy acid **2.70**, the only isolated product is the macrolactone **2.71** but with C7 acylated by 2,4,6-trichlorobenzoyl chloride.[18] Final global deprotection of the macrolactone **2.71** led to the unexpected analogue **2.72** (Scheme 2.14).

In order to preclude the undesired acylation of C7, this hydroxyl needed to be regioselectively protected. Fortunately, we found that Nishiyama-Yamamura previously

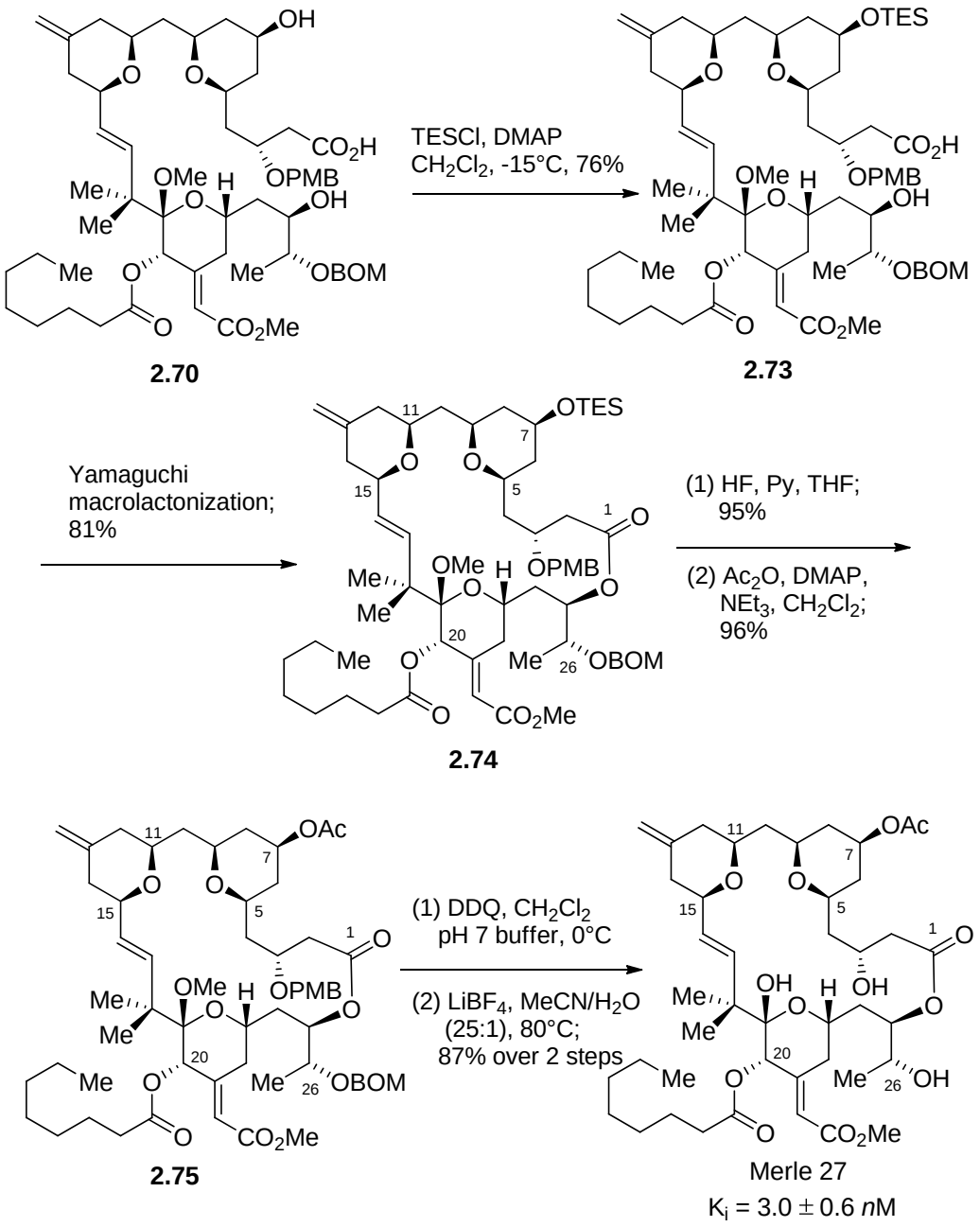


Scheme 2.14 Synthesis of unexpected analogue **2.70**

used 4-dimethylaminopyridine and TESCl at -15 °C to protect the C3 free hydroxyl group in the presence of a free C25 OH and the C1 carboxylic acid in their synthesis of bryostatin 3.[19] The same reaction conditions were applied to substrate **2.70** to deliver the C7-protected seco-acid **2.71**; the Yamaguchi reaction finally delivered the macrolactone **2.72**. Removal of the TES group followed by acetylation gave the desired C7 acetate derivative **2.73**. Finally, protecting group removal by DDQ then $LiBF_4$ in aqueous CH_3CN gave analogue Merle 27 (Scheme 2.15).

The C20 stereochemistry was determined by using a nOe experiment on intermediate **2.72**.[18] A nOe was observed between the equatorial C20 proton and the nearby C34 proton (Figure 2.7). Interestingly, the nOe between C20 proton and C34 proton was not observed in the open-chain intermediate **2.63**.

Both analogues were also submitted to Dr. Blumberg of the NIH for the biological tests. Both compounds proved to have a similar affinity for PKCα to that of bryostatin and Merle 22. The C7 acetate group did not change the binding affinity with PKC dramatically; but the bulky 2,4,6-trichloro benzoate group does lower the affinity about 10 times relative to that of Merle 22. The proliferation and attachment of the U937 leukemia cells test indicated both analogues behaved like PMA instead of bryostatin 1 (Figure 2.8 and 2.9). In the test, both analogues inhibited the proliferation and initiated the attachment of the U937 cell line as did the phorbol ester, while bryostatin 1 showed limited effect on the proliferation and attachment of the U937 cell lines. From the biological test results, we concluded the C7 acetate is not the critical northern hemisphere substituent responsible for the bryostatin-like activity.



Scheme 2.15 Completion of bryostatin analogue Merle 27

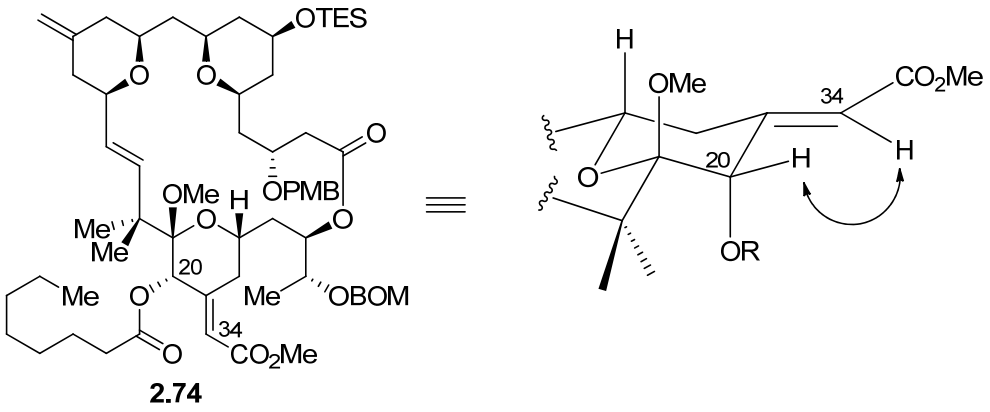


Figure 2.7 Confirmation of stereochemistry on C20 by nOe

Interestingly, among the 12 C7-functionalized derivatives reported by the Wender group, the highest affinity for PKCs was shown by the C7-exomethylene derivative **2.76**.[20] All other modifications at C7 gave materials with decreased affinity for PKCs. The ratio of K_i between C7 exomethylene analogue **2.76** and C7 acetate analogue **2.77** is 2.45. The same is true of the C7 acetate Merle **27** and the C7 trichlorobenzoate analogue **2.72**, which are less potent than the exomethylene compounds Merle **22**. The ratio of K_i between C7 exomethylene analogue Merle 23 and C7 acetate analogue Merle 27 is 2.86. Thus, on both platforms, the exomethylene compounds are approximately 2.5-3-fold more potent in terms of binding than the compounds incorporating the natural C7 acetate functionality (Figure 2.10). From the results of the binding affinity of analogues, we learned that there is a quantitative structure and activity relationship between the C7 substituents and the binding affinity with PKC. We can tune the binding affinity with PKC by changing the substituents on C7 position, which is very helpful for the design of bryostatin analogues in the future.

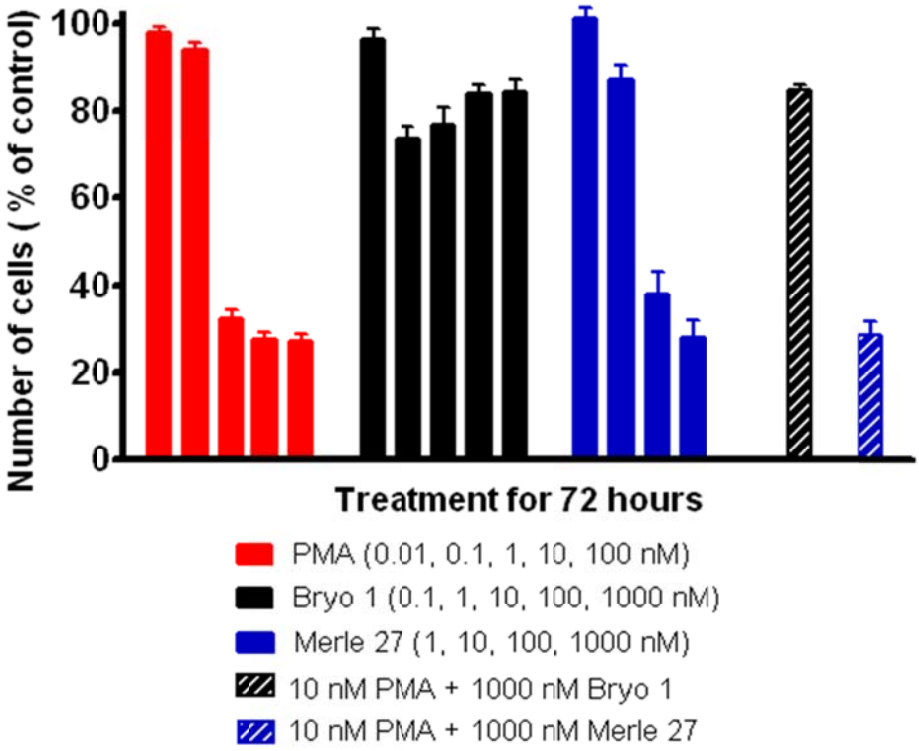


Figure 2.8 U-937 Proliferation Assays with Merle 27

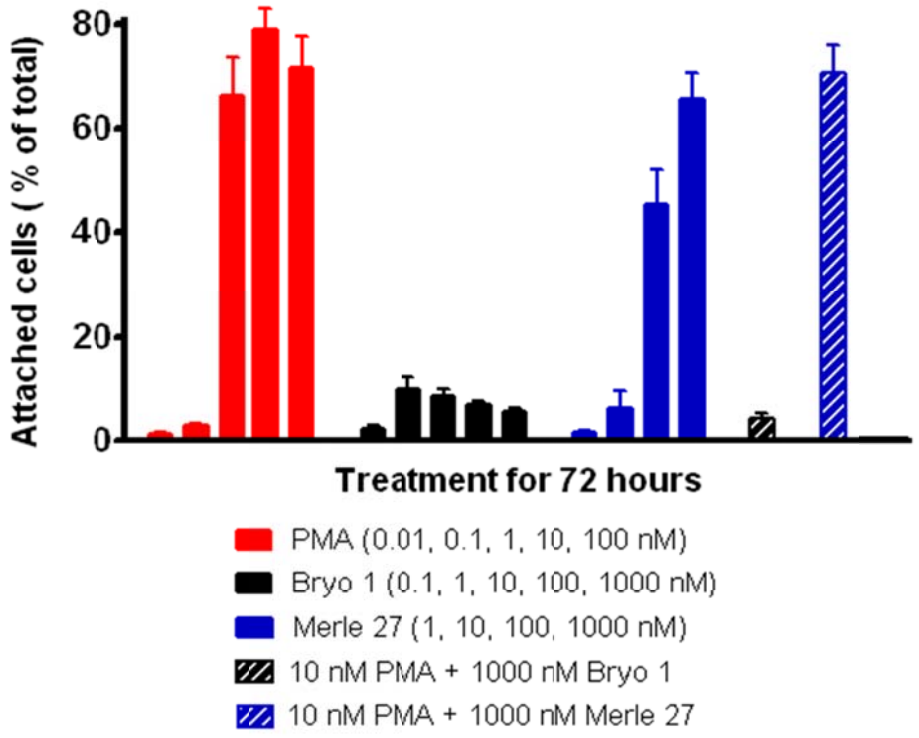


Figure 2.9 U937 Attachment Assays with Merle 27

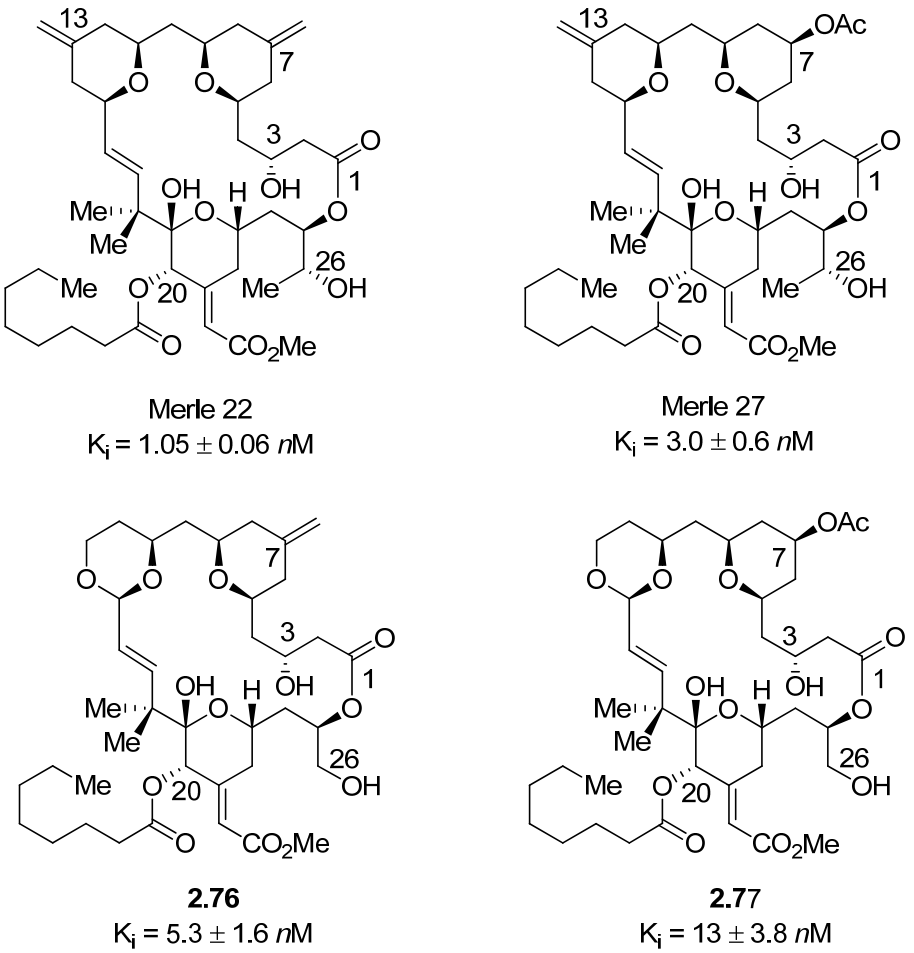
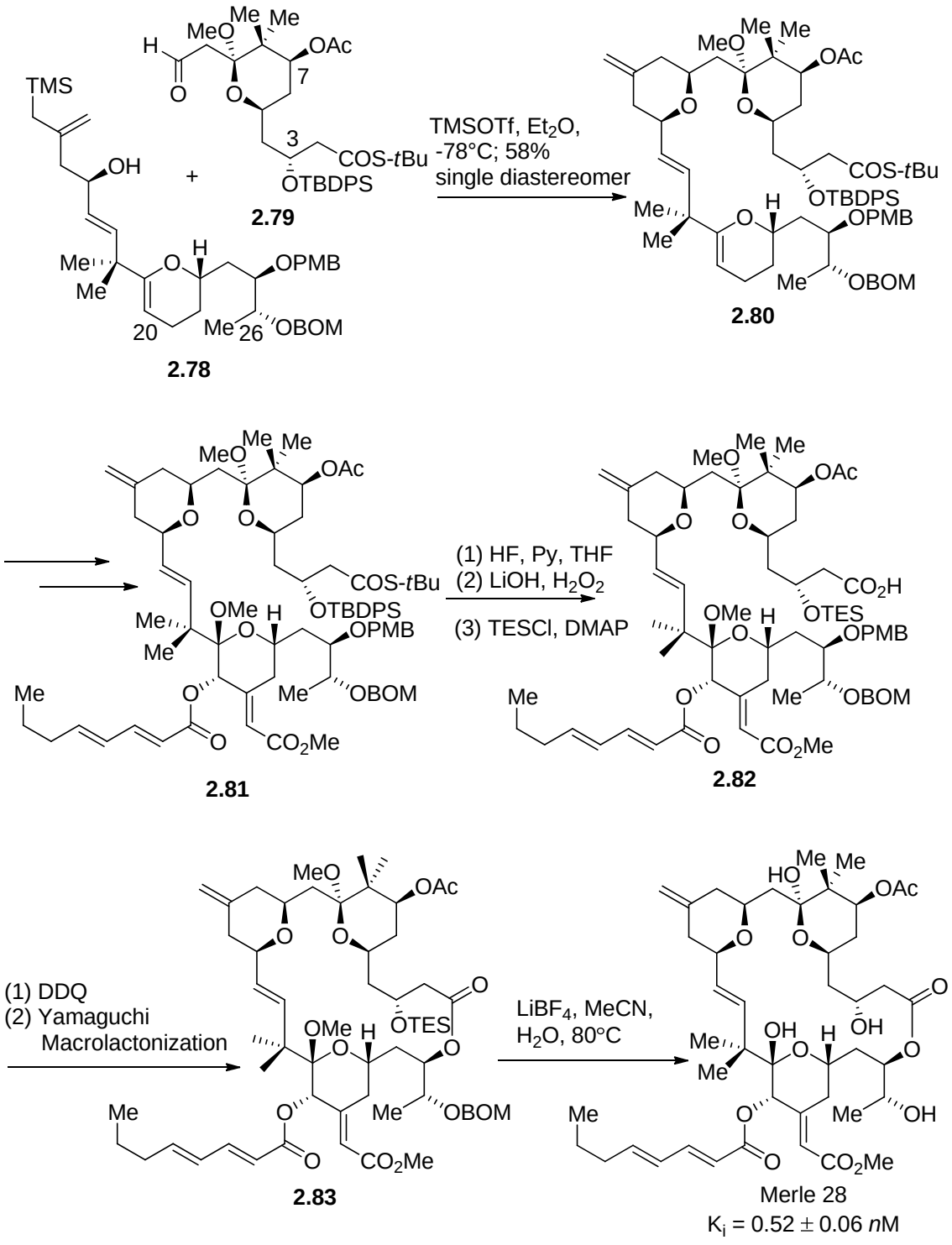


Figure 2.10 Comparison of binding affinitites of bryostatin analogues

While this work was in progress, Dr. Poudel in our group successfully prepared the C30 decarbomethoxy bryostatin 1 analogue.[21] The pyran annulation was used to couple aldehyde **2.78** and hydroxyallylsilane **2.79** to form the tricyclic intermediate **2.80**. Similar steps were chosen to install the functional groups on the C ring to give product **2.81**. The steric hindrance from the bulky TBDPS group on the C3 position makes the hydrolysis of the thioester with hydroperoxide and lithium hydroxide very tedious,

causing the removal of the acetyl group on C7 as well. The deprotection of the TBDPS group at C2 position improved the ensuing hydrolysis of the thioester and afforded the desired carboxylic acid in just one hour without loss of the acetyl group. The free hydroxyl group on the C3 position was then reprotected as the TES ether **2.82**, and the removal of the PMB group on C25 position afforded the seco acid. Yamaguchi reaction conditions were utilized to form the macrolactone **2.83** and global deprotection with $LiBF_4$ gave the analogue Merle 28 (Scheme 2.16).

The biological tests from Dr. Blumberg showed Merle 28 has a high affinity with PKCα ($K_i = 0.52 \pm 0.06$ *n*M). The deletion of C30 ester did not affect the binding affinity. The proliferation and attachment of U937 cell lines indicated that Merle 28 behaved like bryostatin 1 instead of phorbol ester (Figure 2.11 and 2.12). Merle 28 showed limited effect on the proliferation and attachment of U937 cells; furthermore, it antagonized the effect of PMA in high concentration. The finger-print of this response reveals that Merle 28 behaves very much like bryostatin 1. Viewed collectively with the previous results for Merle 27, these results clearly show that: (1) the C7 acetate or C30 carbomethoxy group alone is not essential to obtain bryostatin-like biological responses with these analogues; the deletion of C30 carbomethoxy group or the installation of C7 acetate does not switch the bioactivity of bryostatin analogues between bryostaitn-like and phorbol-like, and (2) the C9 OH and/or the C8 *gem*-dimethyl group may be critical in conferring bryostatin-like biological responses as opposed to those characteristic of the tumor-promoting phorbol esters. The next target molecule in our study would be focus on the preparation of bryostatin analogue without the C9 OH or the C8 *gem*-dimethyl group.



Scheme 2.16 Poudel's Synthesis of C30 decarbomethoxyl analogue Merle 28

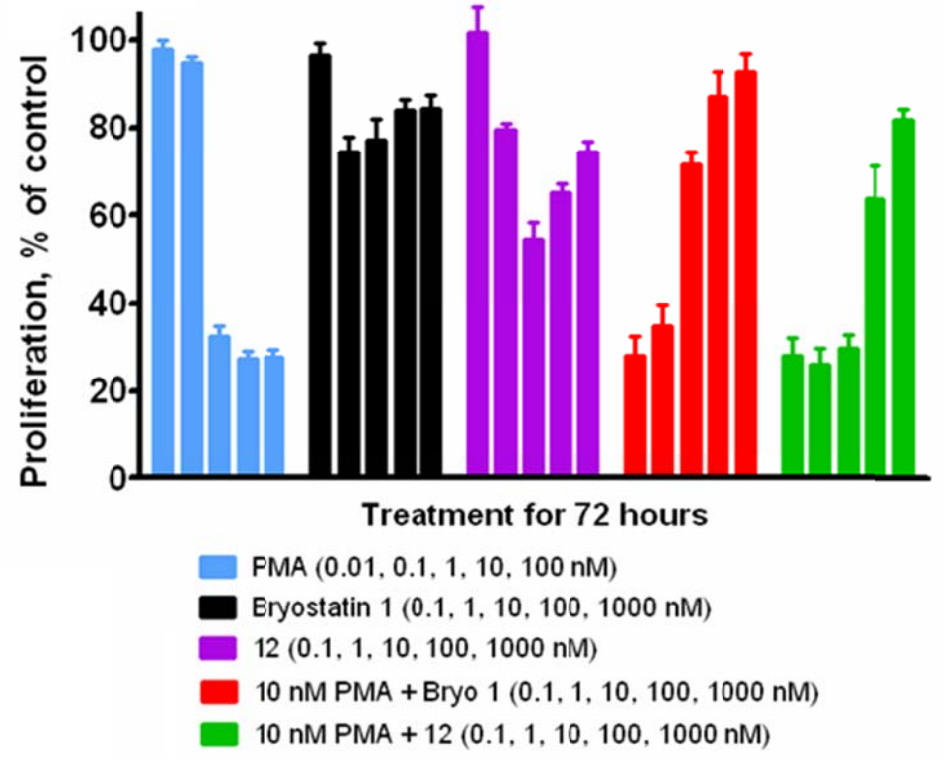


Figure 2.11 U937 proliferation assay with Merle 28

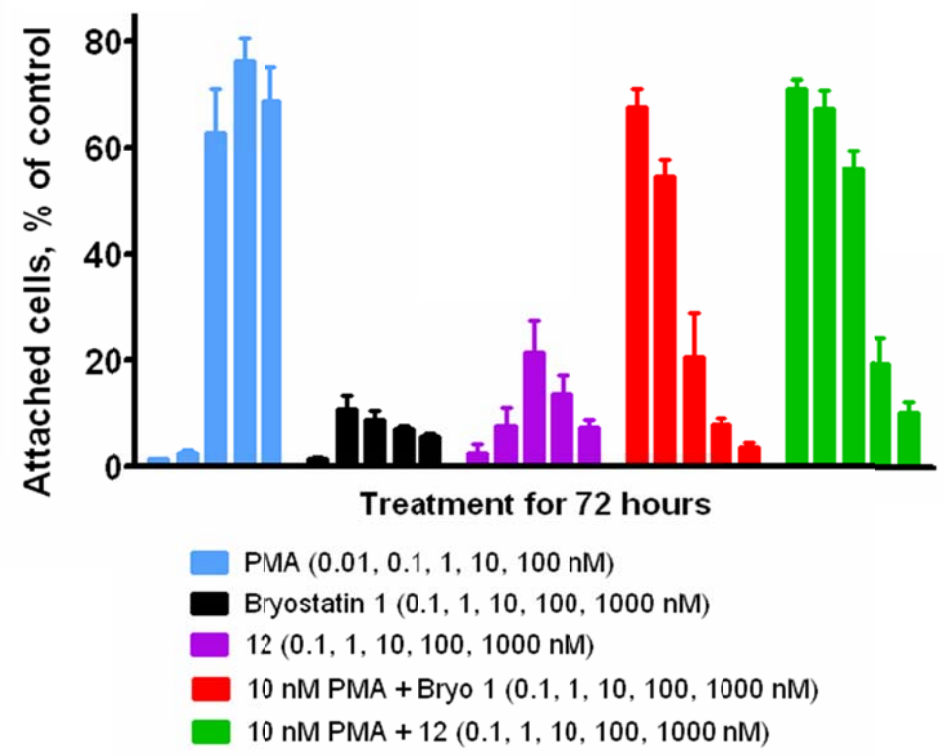
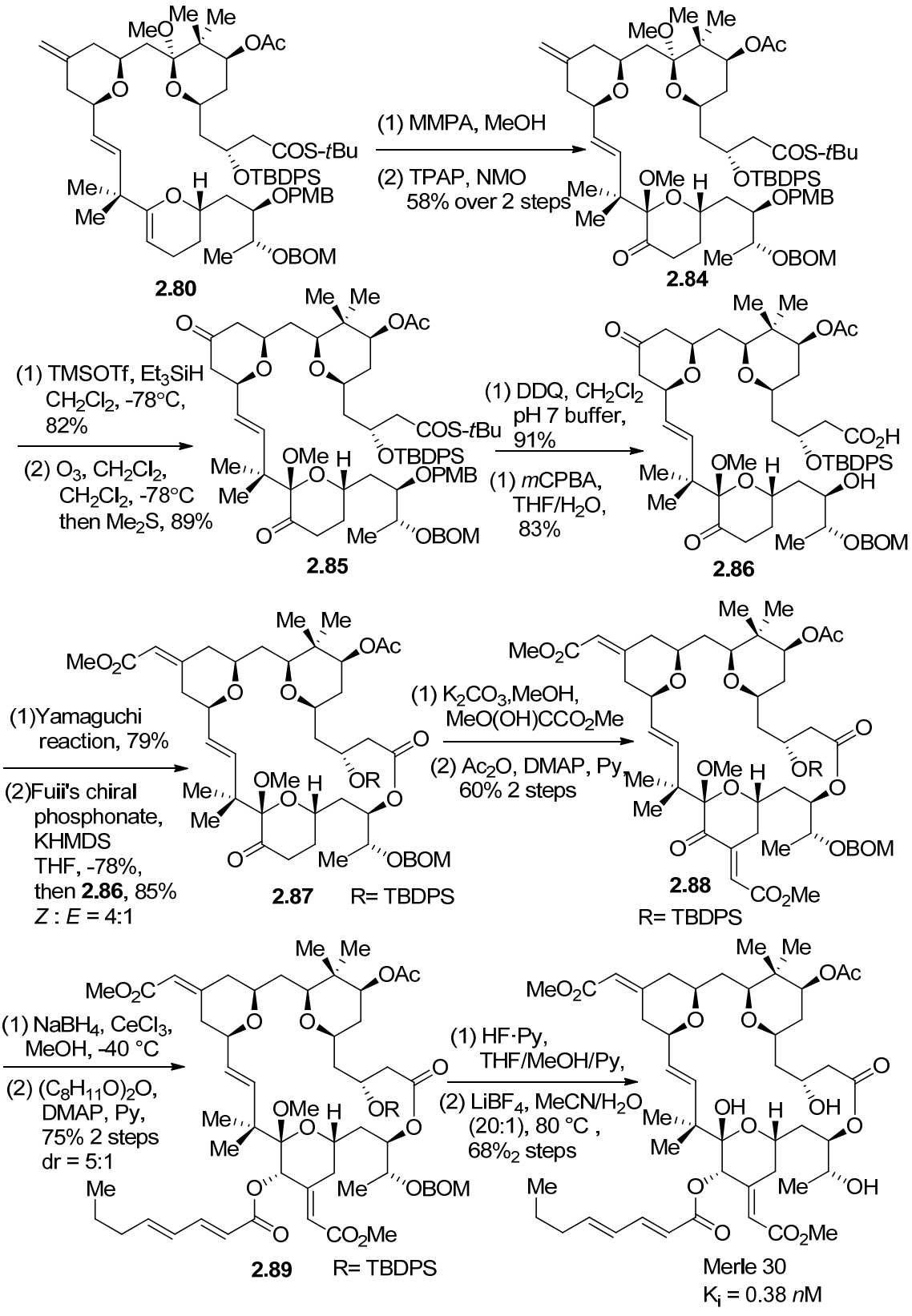


Figure 2.12 U937 attachment assay with Merle 28

Dr. Poudel also completed the synthesis of C9 deoxy bryostatin 1 analogue (Scheme 2.17).[22] The common intermediate glycal **2.78** was sequentially oxidized by magnesium monoperoxyphthalate (MMPP) and TPAP/NMO to afford the α-ketone ketal **2.84**. The hemiketal on the C9 position was selectively reduced by Et_3SiH in the presence of TMSOTf. Ozonolysis regioselectively cleaved the olefin on the C13 position to afford the ketone **2.85**. The removal of the PMB group on the C25 position with DDQ and hydrolysis of the thiol ester using *m*CPBA in aqueous THF afforded the seco acid **2.86** in good yield. The hydrolysis of the thioester with *m*CPBA proved to be selective for the thiolester without any hydrolysis of the C19 methyl ketal or Baeyer-Villiger oxidation of the B or C ring ketones. Yamaguchi macrolactonization of the resulting seco acid **2.86** then afforded the macrolactone, and an asymmetric Horner-Emmons reaction using a chiral phosphonate with ketone on the C13 position provided a 4:1 mixture of *Z*/*E* olefin isomers.[23] The C20 ketone in **2.87** underwent an aldol reaction with methyl glyoxylate and K_2CO_3; C7 acetyl group was also removed during the reaction and was reinstalled during the elimination reaction with Ac_2O and pyridine to give enone **2.88**. Luche reduction and esterification finished the modifications on the C ring to deliver the precursor **2.89** with a 6:1 mixture of diastereomers. The final deprotection was achieved with the treatment of HF/Py, followed by $LiBF_4$ in $MeCN/H_2O$ at 80 °C, affording the final product Merle 30.

The biological test on U937 cell line showed Merle 30 has a high affinity with PKC (K_i = 0.38 ± 0.07 *n*M). The deletion of the C9 hydroxyl group does not affect the binding affinity. The proliferation and attachment of U937 cell lines indicated Merle 30



Scheme 2.17 Poudel's synthesis of analogue Merle 30

behaved like bryostatin 1 instead of phorbol ester (Figure 2.13 and 2.14). Merle 30 showed limited effect on the proliferation and attachment of U937 cells; furthermore, it antagonized the effect of PMA in high concentration. The profile of response suggests that Merle 30 behaves like bryostatin 1.

The biological activity of Merle 30 was also examined in another system, the androgen-dependent human prostate cancer cell line LNCaP, for two different endpoints: proliferation and secretion of tumor necrosis factor α (TNFα), a key mediator of inflammation. In this system, PMA inhibited cell proliferation and induces apoptosis whereas bryostatin 1 does not. Merle 30 behaved almost identically to bryostatin 1; it did not inhibit LNCaP proliferation but antagonized the inhibition by PMA (Figure 2.15). For induction of TNFα secretion, the three agents behaved differently: PMA induced a potent response, bryostatin 1 induced no response, and Merle 30 induced a weak biphasic response (Figure 2.16). Once again, bryostatin 1 and Merle 30 blocked the response to PMA. Although there is clearly some effect due to the deletion of the C9 OH, we conclude that the C9 hydroxyl of bryostatin 1 makes only a minor specific contribution to the unique patterns of biological response to bryostatin 1.

It has been suggested by the Itai group that the C9 OH might be a key structural feature based in their computational study. The docking study between simplified bryostatin 1 structure with X-ray structure of PKCδ C1 domain suggested that there are four hydrogen bonds existing during the binding of bryostatin with C1 domain. One of them occurs between the C9 OH and the carbonyl of Met239 in the PKCδ C1 domain. The biological results suggest that the proposed hydrogen bonding between the C9 OH and Met 239 is not necessary to realize high affinity binding with PKC.

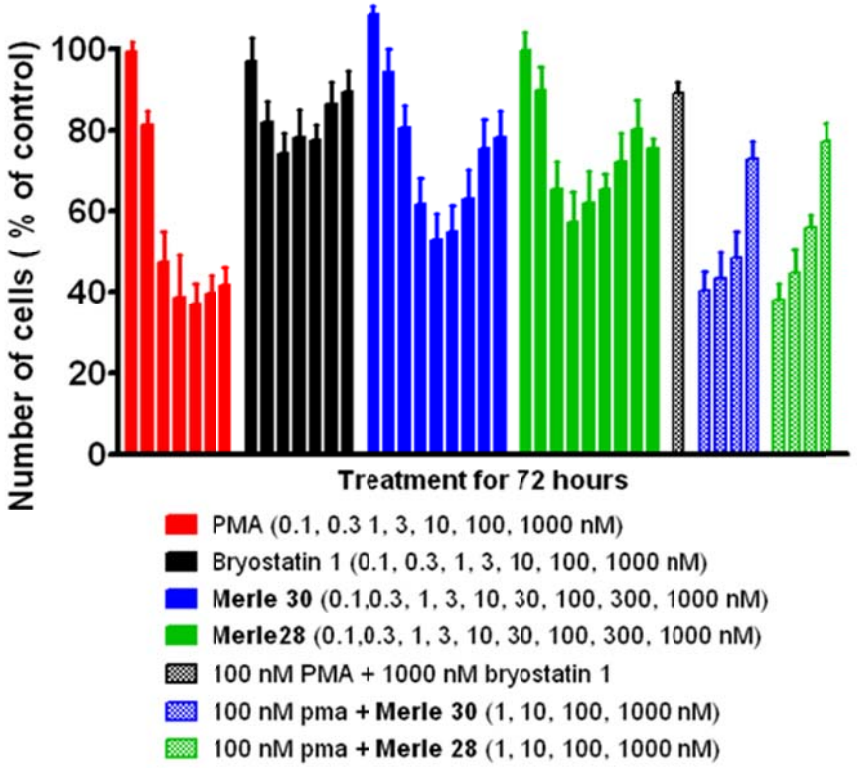


Figure 2.13 U937 proliferation assay with Merle 30

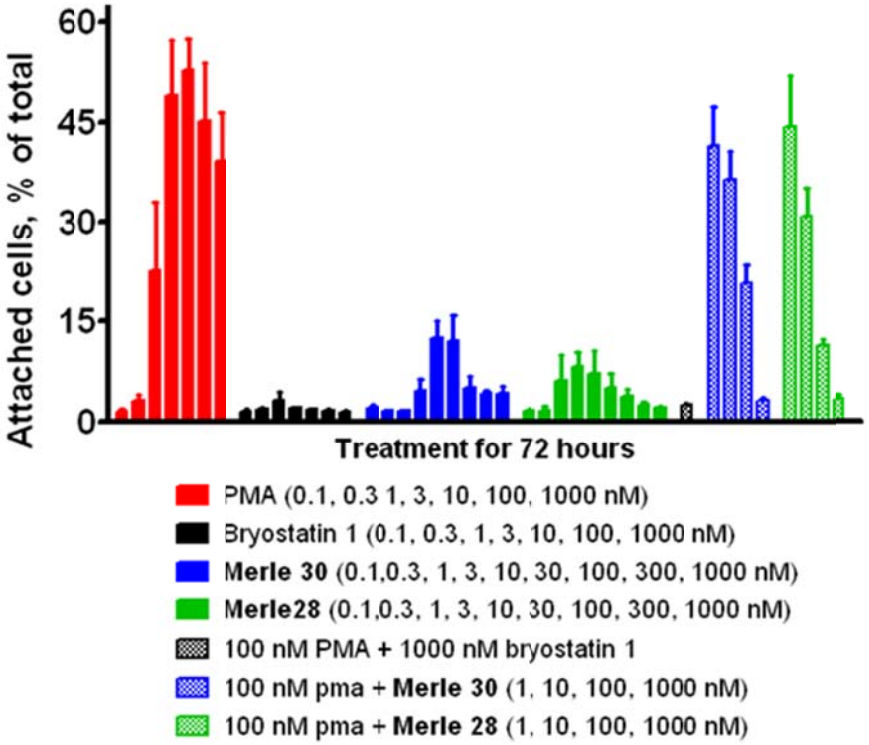


Figure 2.14 U937 attachment assay with Merle 30

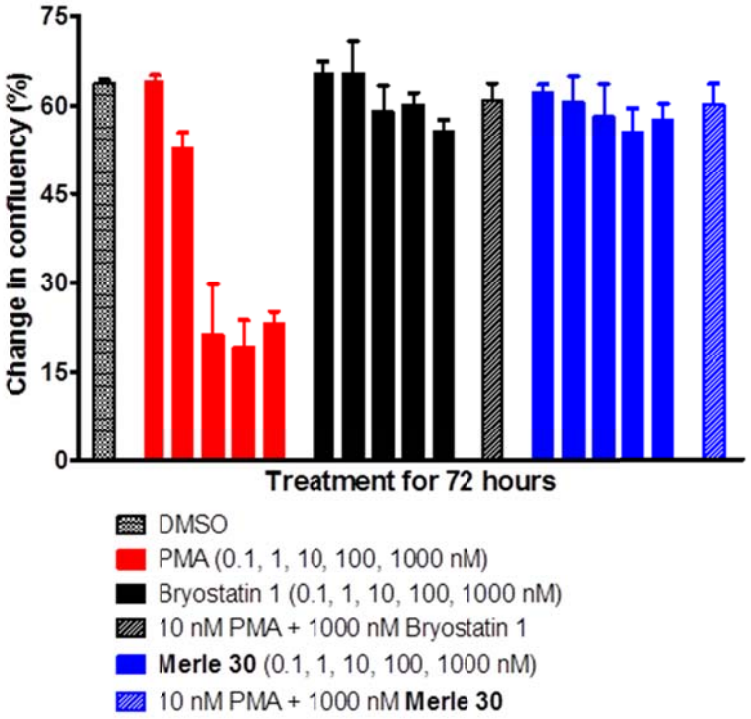


Figure 2.15 Proliferation assay of LNCaP cells with Merle 30

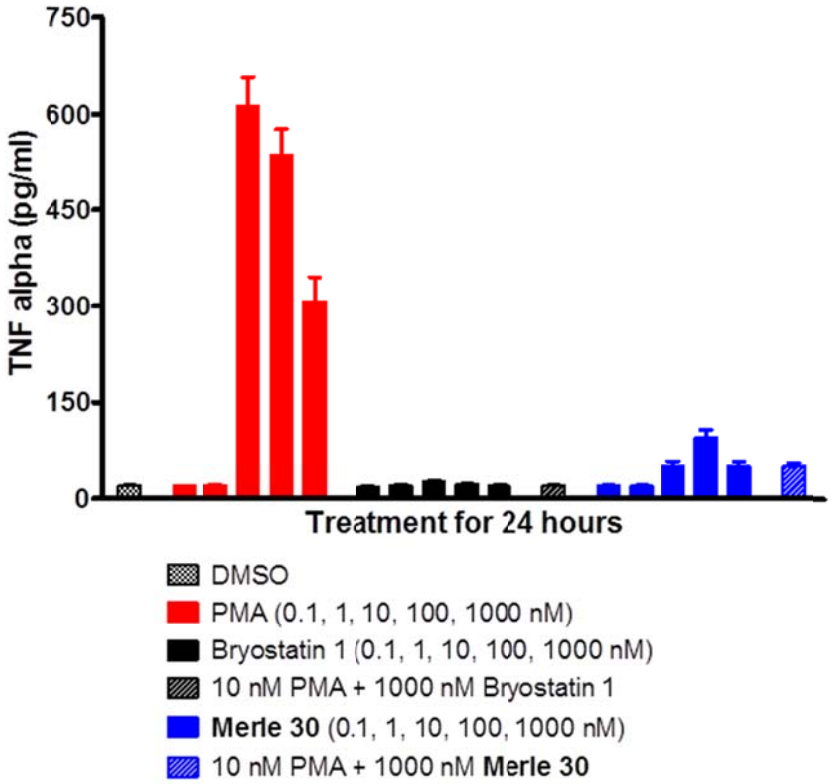


Figure 2.16 Secretion of TNF-alpha from LNCaP cells with Merle 30

Synthetic and Biological Study of Bryostatin Analogue With C7 Acetate and C13 Enoate

When all the bryostatin analogues prepared are viewed collectively, we find that the deletion of the the C30 carbomethoxyl or C9 OH substituent does not switch the bryostatin-like bioactivity into phorbol-like activity; moreover the installation of the C7 acetate alone does not render the analogue with bryostatin-like activity. It is possible that no single functional group on the A and B pyran rings is responsible for the unique bioactivities of bryostatin 1, which may be based on the cooperation or well-balanced physico-chemical properties among those substituents. When we divide all the analogues examined into two groups as bryostatin-like and PMA-like, we can find (1) all the PMA-like analogues have no polar group or only one polar group on the northern hemisphere; (2) all the bryostatin-like analogues and bryostatin 1 have 2 or more polar groups in the same region (Figure 2.17).

Additionally, the membrane translocation of PKCs is considered as the hallmark of PKC activation. The Blumberg group reported that tumor-promoting PMA translocates PKC to the plasma membrane in CHO-K1 cells, while bryostatin 1 mainly translocates it to the nuclear membrane.[24] They suggested the lipophilicity of PKC ligands to be a critical factor that controls the cellular localization of PKCH0 δ.[25] Hydrophobic ligands, such as PMA, tended to translocate PKC to the plasma membrane, whereas more hydrophilic ligands, such as bryostatin 1, moved it to the nuclear membrane. It is not known how the localization of PKCδ is related to the anticancer activity associated with bryostatin 1, but tuning the hydrophobicity of PKC ligands may help answer the question.

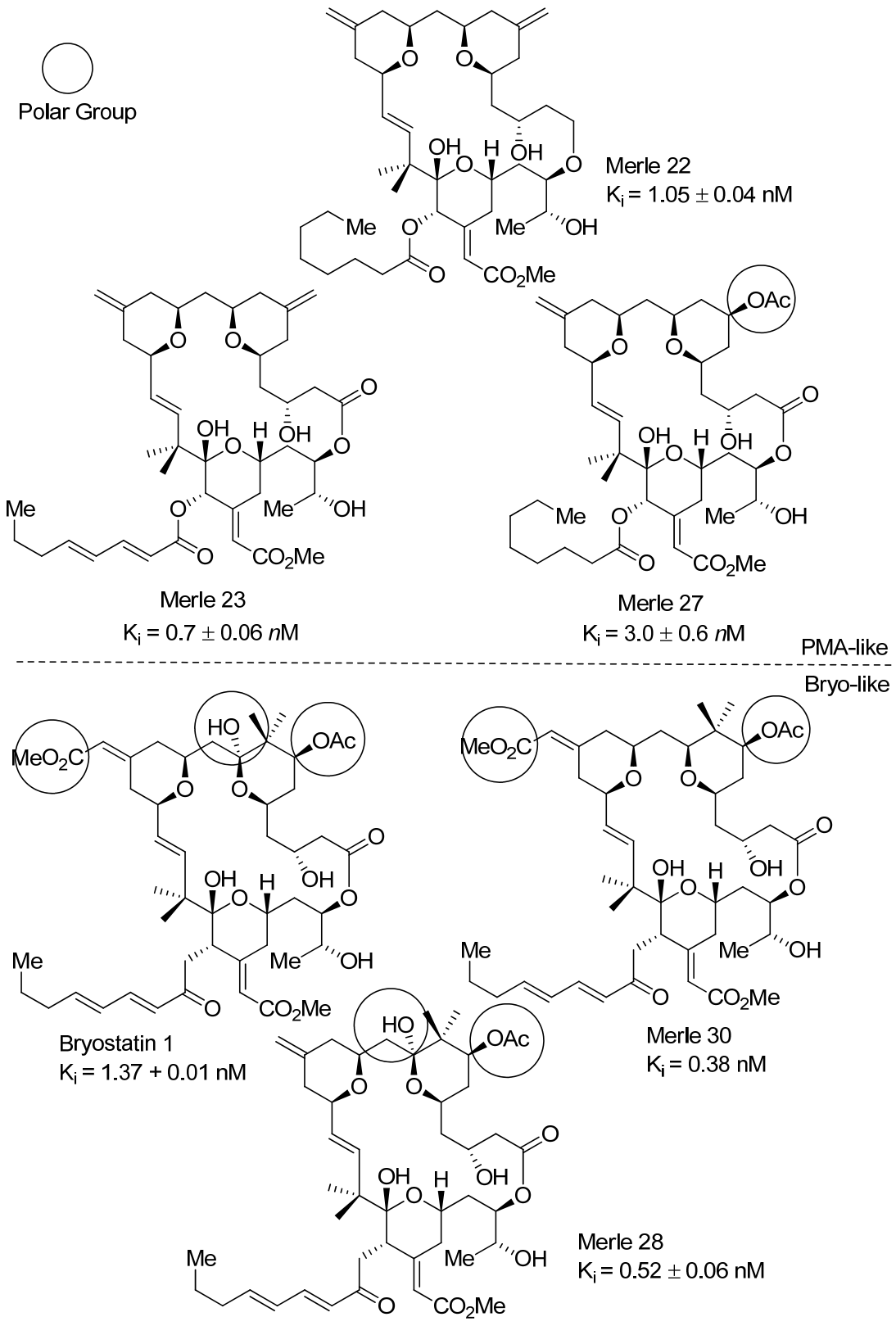


Figure 2.17 The Comparison of Bryostatin Analogues

These results encouraged us to pursue the synthesis of the next bryostatin analogue with both C7 acetate and C13 enoate substituents. Based on the biological results from Merle 27 and Merle 28, the C7 acetate or C13 enoate alone does not determine the analogue behave biologically PMA-like or bryostatin-like. We expected that the synthesis of analogue **2.90** with both C7 acetate and C13 enoate would reveal the biological response of a simplified analogue with two polar groups. The retrosynthetic analysis of analogue **2.90** is outlined in Figure 2.18. We anticipated the analogue **2.90** could be prepared from the advanced intermediate **2.91**.

The intermediate **2.91** is expected from the pyran annulation between the hydroxyallylsilane **2.57** and the aldehyde with fully functionalized C ring **2.92**. The advantages of the fully functionalized C-ring moiety are expected in (1) making the whole synthesis of the bryostatin analogue more convergent and efficient by reducing the steps after coupling the two complex moieties; (2) avoiding the possible problems during the installation of substituted group on C ring in the late stage, which include the undesired side reaction during the aldol reaction and elimination, and modest diastereoselectivities during the Luche reduction; (3) it can applied into synthesis of different bryostatin analogues and total synthesis natural bryostatins.

The aldehyde with fully functionalized C ring **2.92** was envisioned to be synthesized from ketone **2.93**. The protected alcohol on C16 position instead of carbonyl was anticipated to avoid the undesired Michael addition to the α,β-unsaturated carbonyl based on our previous experience. The ketone **2.93** was expected to be available from the known olefin **2.25**.

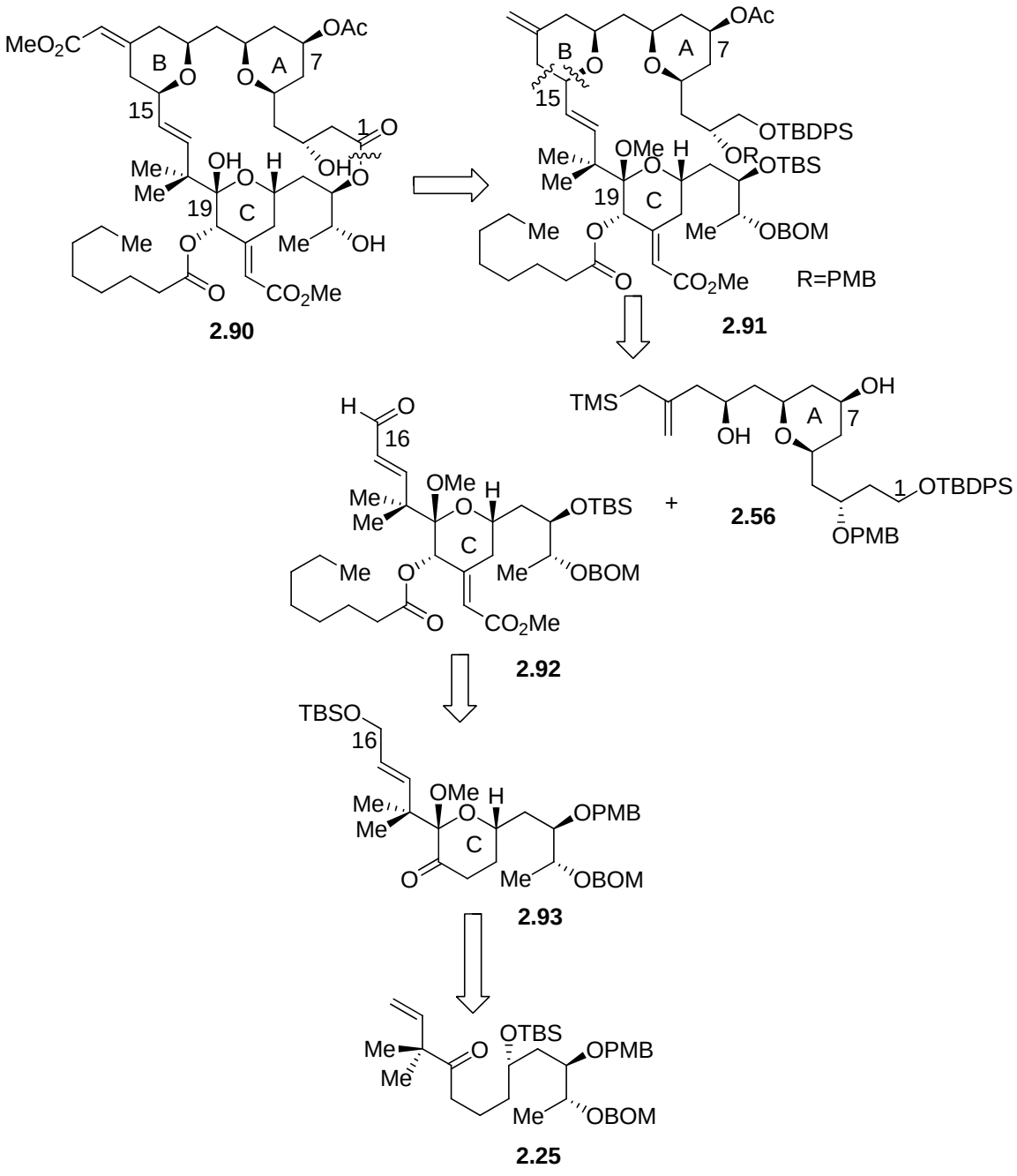
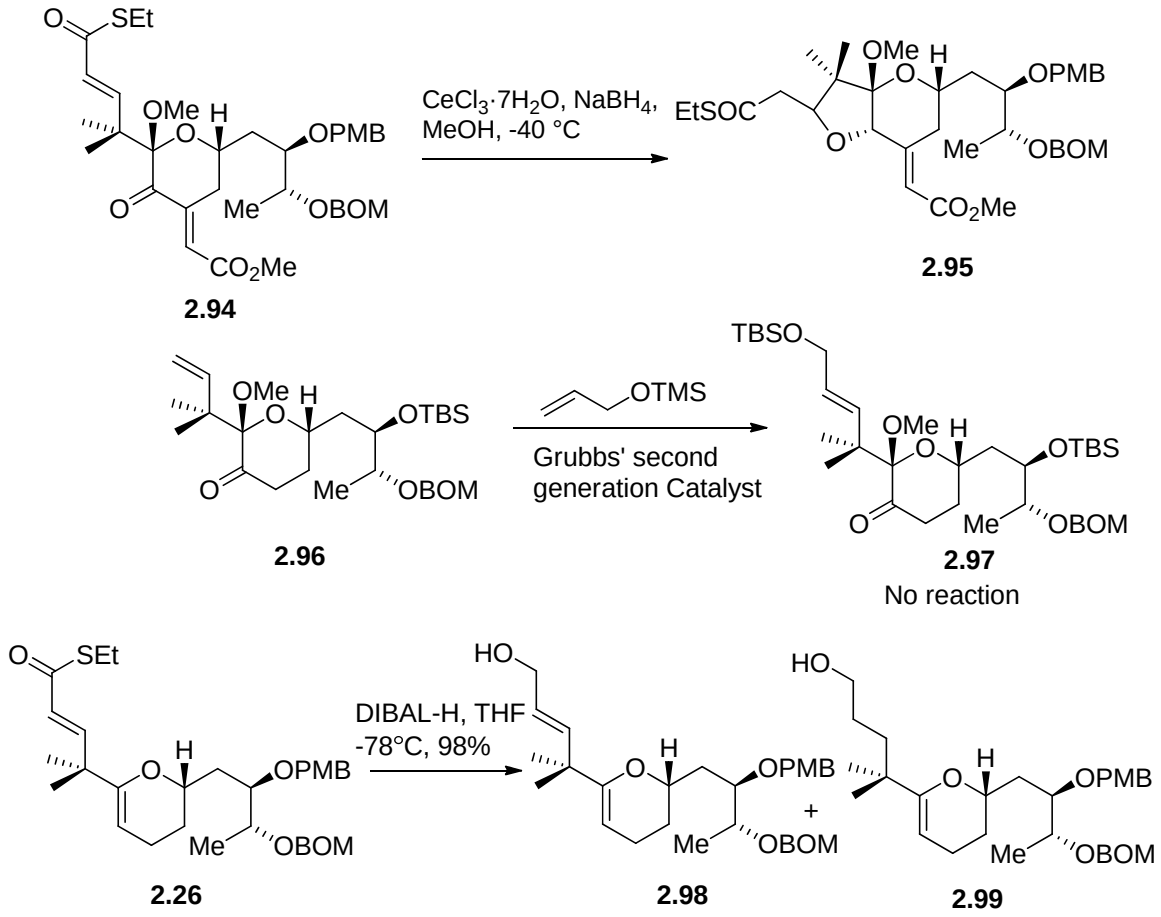


Figure 2.18 Retrosynthesis of Bryostatin Analogue **2.88**

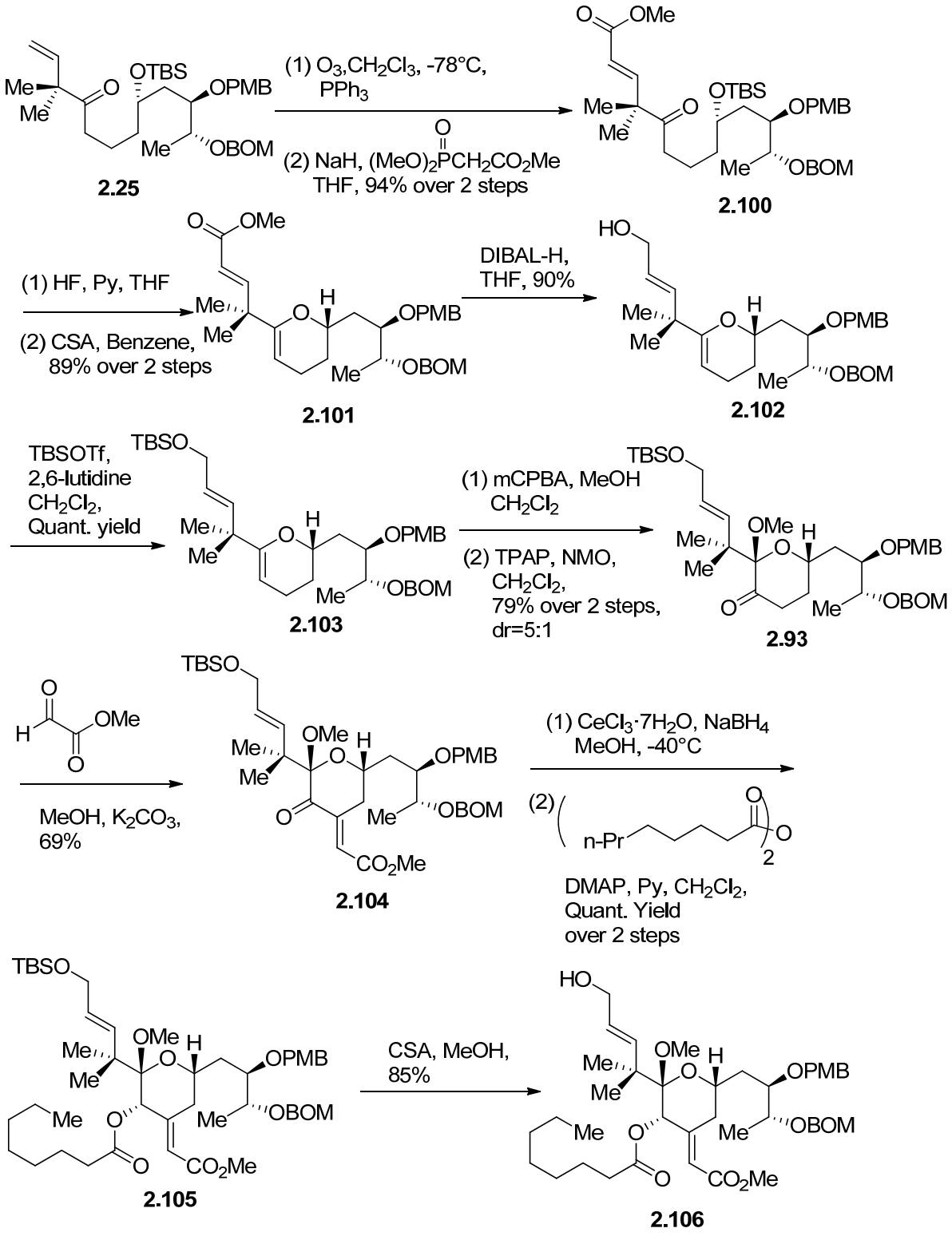
The failed attempts to the aldehyde **2.92** are summarized in Scheme 2.18. The Luche reduction on ketone **2.94** initiated Michael addition of the resulting C19 alcohol to the *α,β*-unsaturated thioester in situ to afford **2.95** before any acetylation could be applied on the alcohol. Another attempt of cross metathesis between olefin **2.96** and allylic alcohol TMS ether failed to afford the desired product **2.97**, primarily due to the steric effect of *gem*-dimethyl group.[26,27] Attempts to reduce thioester **2.26** with diisobutylaluminium hydride gave an inseparable mixture of 1,2-reduced product **2.98** and fully reduced product **2.99** in a ratio of 4:1.



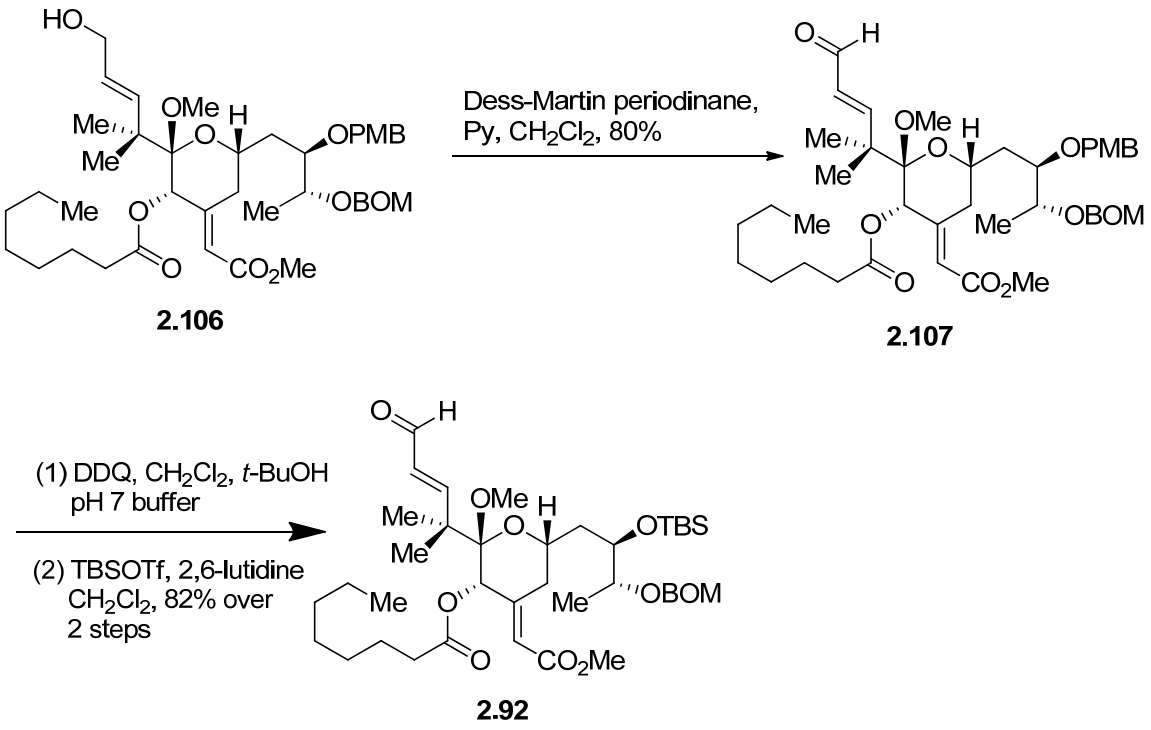
Scheme 2.18 Attempted routes to fully functionized C ring aldehyde **2.90**

In order to eliminate the undesired 1,4-reduction on α,β-unsaturated thioester **2.26**, we expected of the oxo-ester would increase the regioselectivity during the reduction. In practice, we started with olefin **2.25** (Scheme 2.19**)**, which was oxidatively cleaved by ozonolysis and was transformed into α,β-unsaturated oxo-ester **2.100** through a Horner-Emmons reaction. Deprotection of the TBS ether using HF/py buffer, and subsequent cyclization and dehydration promoted by CSA in benzene gave the desired glycal **2.101**. The ester in **2.101** was reduced to the allylic alcohol **2.102** without the formation of any fully reduced byproduct with diisobutylaluminium hydride, and the resulting alcohol was protected as a TBS ether **2.103**. The sequential epoxidation with *m*CPBA and Ley oxidation with TPAP and NMO afforded the ketone **2.93** in 79% yield with a diastereoselectivity of 4:1 at the C19 hemi-ketal favoring the desired isomer. Fortunately, the mixture of diastereomers could be separated by flash chromatography. The aldol reaction and elimination could be performed in one pot with freshly prepared glyoxylate and K_2CO_3 to give the enoate **2.104** in good yield.[28] The C20 ketone on **2.104** was reduced via Luche conditions and the resulting alcohol was immediately acylated to afford the product **2.105**. Deprotection of the TBS group led to the primary alcohol **2.106**.

The alcohol **2.106** was oxidized using Dess-Martin periodinane, resulting in the formation of aldehyde **2.107**. Due to the fact that there was a PMB group on the C3 position of hydroxyallylsilane **2.57**, the PMB group on the C25 position of **2.107** was swapped with a TBS group in order to avoid having two PMB protecting groups in the pyarn annulation product. The final steps included the deprotection of the PMB group at C25 and reprotection as the TBS ether to give the aldehyde **2.92** (Scheme 2.20).



Scheme 2.19 Synthesis of Fully functionalized C ring aldehyde **2.90**



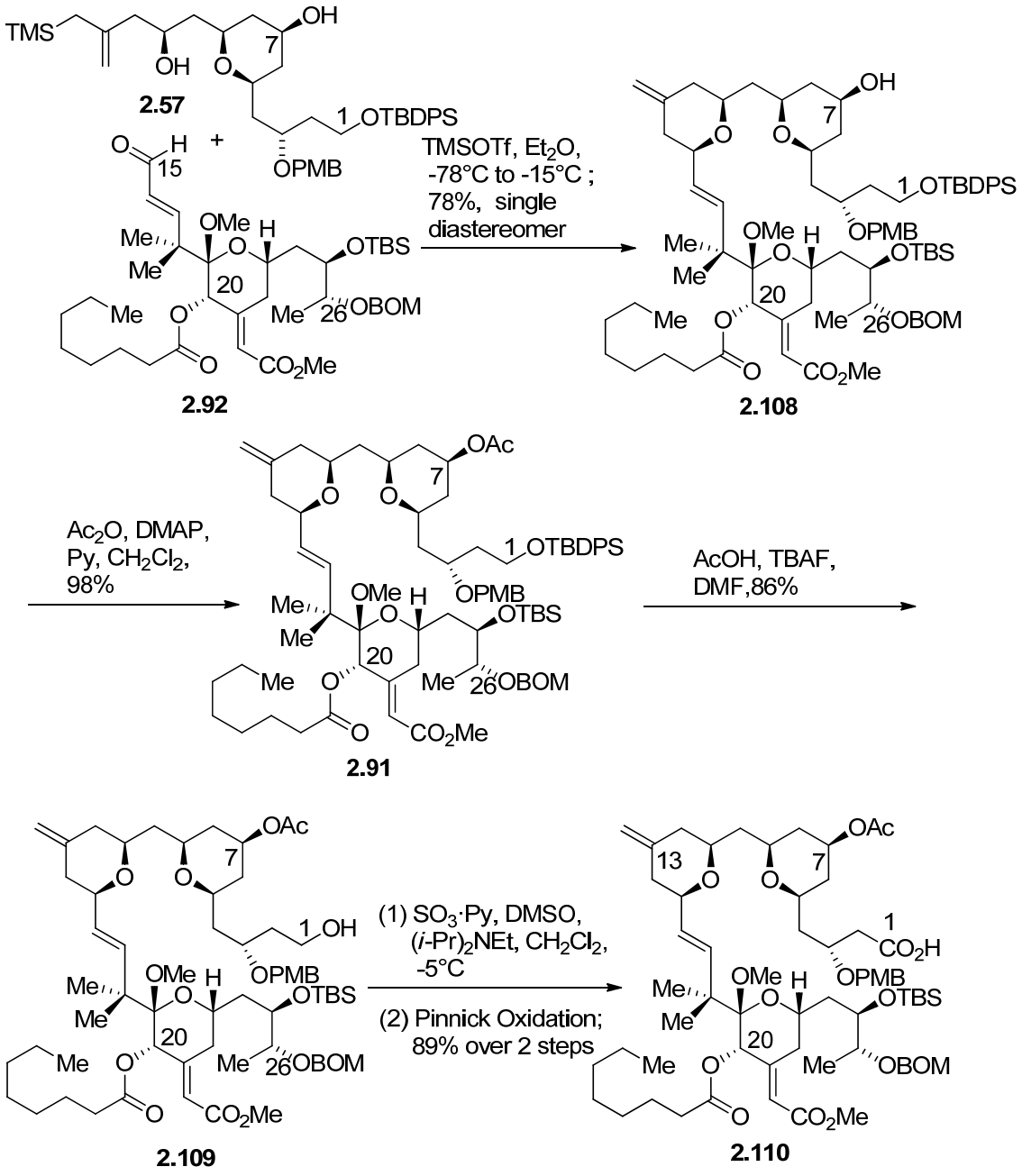
Scheme 2.20 Synthesis of Fully functionalized C ring aldehyde **2.92**

The pyran annulation between aldehyde **2.92** and hydroxyallylsilane **2.57** smoothly afforded the product **2.108** in good yield (Scheme 2.21). It was noticed that the reaction was slower than the previous pyran annulation reactions. The pyran annulation reaction between aldehyde **2.37** and hydroxyallylsilane **2.57** in the synthesis of Merle 27 took only 1 h to complete at -78 ºC, while the pyran annulation with fully functionalized C ring was not complete after 6 h at -78 ºC. Fortunately, we found that elevated temperature could increase the rate of the reaction. After 2 h at -78 ºC, the reaction was warmed to -15 ºC and kept for 1 h to push the reaction to completion.

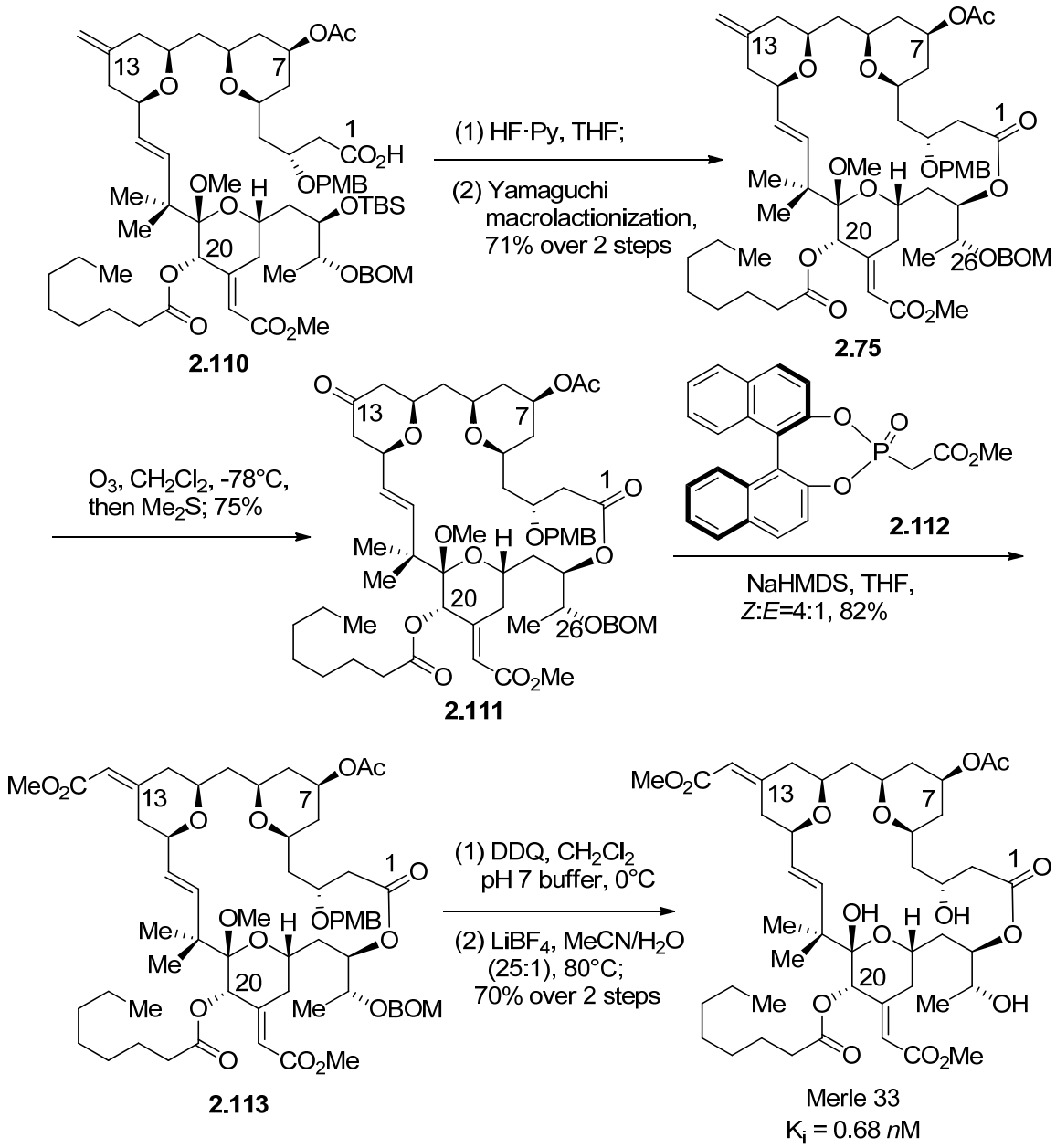
The C7 free hydroxyl group was acetylated to give tricyclic product **2.91**. The deprotection of TBDPS group at C1 position with TBAF and AcOH afforded the primary alcohol **2.109**, which was exposed to sequential Parikh-Doering and Pinnick oxidation

conditions to afford the carboxylic acid **2.110. T**he removal of the TBS group with HF/Py gave the seco acid, which was subjected to Yamaguchi macrolactonization conditions to deliver macrolactone **2.75**. The olefin at C13 was cleaved by careful addition of a solution of ozone in CH_2Cl_2 at -78 ºC, and the resulting ketone **2.111** was subjected to an asymmetric Hormer-Emmons reaction with Fuji's chiral phosphonate **2.112** to afford a 4:1 mixture of *Z*:*E* diastereomers **2.113**.[18,29] The global deprotection then afforded the bryostatin analogue Merle 33 (Scheme 2.22).

The biological tests from Dr. Blumberg showed Merle 33 has a high affinity with PKCα ($K_i = 0.68 \pm 0.01$ *n*M). The installation of the enoate at the C13 renders the bryostatin analogue a slightly better affinity binding with PKC. The proliferation and attachment of U937 cell lines supported our initial hypothesis that the analogue with two or more polar groups on the northern hemisphere behaviours likes bryostatin 1 (Figure 2.19 and 2.20). The results indicated that Merle 33 demonstrated a similar response during the proliferation and attachemtn of U937 cell line as Merle 30 did. Merle 33 showed limited effect on the proliferation and attachment of U937 cells; furthermore, it antagonized the effect of PMA in high concentration. The profile of response suggests that Merle 33 behaves like bryostatin 1. The results revealed Merle 33 behaved close to phorbol ester in low concentration, but behaved like bryostatin 1 in high concentration instead of the phorbol esters (Figure 2.11 and 2.12). The bryostatin-like response from Merle 33 excluded the possibility that the C8 gem dimethyl group is the critical substituent, which will be very helpful for the future work on the synthesis of bryostatin analogues. Currently our group is working on the synthesis of other bryostatin analogues to undertand the role of the substituents on the biological activities of bryostatin 1.



Scheme 2.21 Synthesis of bryostatin analogue



Scheme 2.22 Completion of bryostatin analogue Merle 33

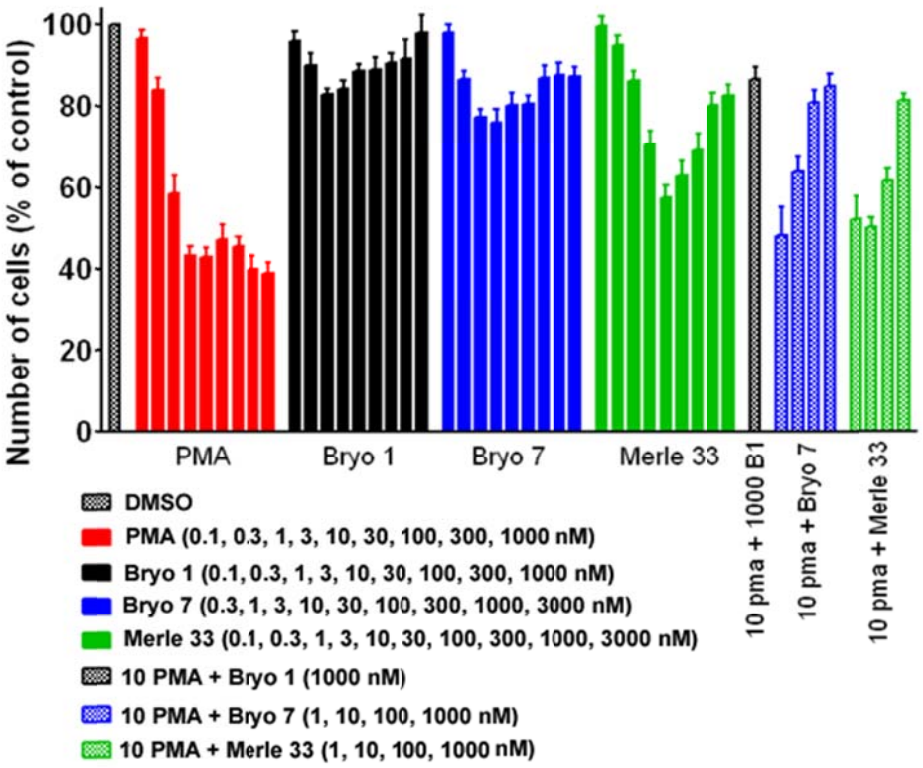


Figure 2.19 U937 proliferation assay with Merle 33

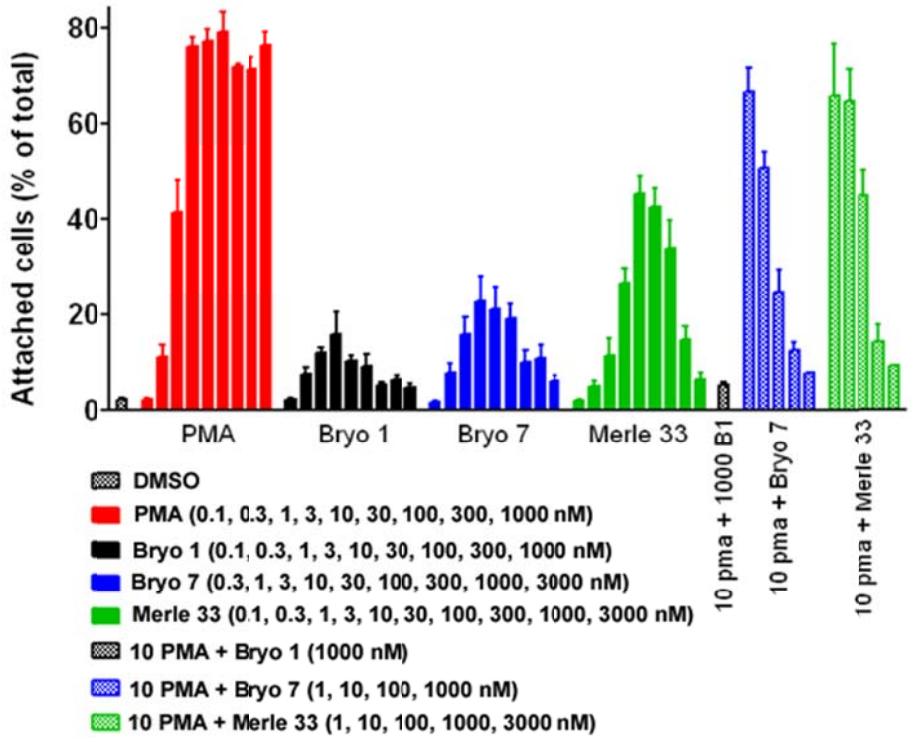


Figure 2.20 U937 proliferation assay with Merle 33

Conclusion

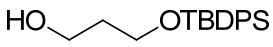
The structurally simplified bryostatin analogues were prepared in a convergent manner by utilization of the pyran annulation methodology developed in our group. During the synthesis of analogue Merle 27, the functionalization on C ring before the formation of the macrolactone demonstrated better yields and diastereoselectivities in the steps of functionalization on the C ring. The biological studies of Merle 27 showed its high binding affinity with PKC similar to that of bryostatin 1, but the results from the proliferation and attachment assay of the U937 cell line suggested that Merle 27 behaved like the tumor promoter PMA instead of like bryostatin 1, which excludes the C7 acetate alone as playing a critical role in defining the unique biological activities of bryostatin as an antagonist to phorbol esters.

In order to identify the pharmacophoric groups in the northern hemisphere of bryostatin 1 responsible for its unique biological activities, the bryostatin analogue Merle 33 with C7 acetate and C13 was prepared through a pyran annulation involving the fully functionalized C ring aldehyde. The fullyl functionalized C ring aldehyde **2.92** not only made the whole synthesis more convergent and efficient, but also eliminated tedious protection and deprotection steps on C7 position. The biological results of analogue, Merle 33, revealed that the installation of C13 enotate on B ring switched the biological response from PMA-like to bryostatin-like. This change supports our hypothesis that the biological activities of bryostatin analogues are affected by the polarity of the northern hemisphere. The further study of how the polarity groups or polarity in the northern hemishpre of bryostatin analogues affect the biologic response of analogues will be the focus of our future research.

Experimental Section

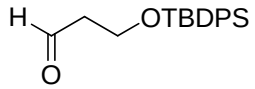
Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966).[30] Diisopropylamine, diisopropylethylamine, pyridine, triethylamine, EtOAc, MeOH, and CH_2Cl_2 were distilled from CaH_2. The titer of *n*-BuLi was determined by the method of Eastham and Watson.[31] All other reagents were used without further purification. Yields were calculated for material judged homogenous by thin layer chromatography and nuclear magnetic resonance (NMR). Thin layer chromatography was performed on Merck Kieselgel 60 Å F254 plates or Silicycle 60Å F254 eluting with the solvent indicated, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 12-molybdophosphoric acid, or 4-anisaldehyde. Flash chromatography was performed with Silicycle Flash Silica Gel 40 – 63 μm or Silicycle Flash Silica Gel 60 – 200 μm, slurry packed with 1% EtOAc/hexanes in glass columns. Glassware for reactions was oven dried at 125 °C and cooled under a dry nitrogen atmosphere prior to use. Liquid reagents and solvents were introduced by oven dried syringes through septum-sealed flasks under a nitrogen atmosphere. Nuclear magnetic resonance spectra were acquired at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million relative to the signal of relative to the signal of residual $CHCl_3$ at 7.27 ppm. Chemicals shifts for carbon nuclear magnetic resonance (^{13}C NMR and DEPT) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 77.23 ppm. Chemical shifts of the unprotonated carbons ('C') for DEPT spectra were obtained by comparison with the ^{13}C NMR spectrum. The abbreviations s, d, apd, dd, ddd, dddd, ddddd, dddddd, t, td, tt, q, dq,

bs, and m stand for the resonance multiplicity singlet, doublet, apparent doublet, doublet of doublets, doublet of doublet of doublets, doublet of doublet of doublet of doublets, doublet of doublet of doublet of doublets of doublets, doublet of doublet of doublet of doublets of doublets of doublets, triplet, triplet of doublets, triplet of triplets, quartet, doublet of quartets, broad singlet, and multiplet, respectively. Optical rotations (Na D line) were obtained using a microcell with 1 dm path length. Specific rotations ([α], Unit: °cm^2/g) are based on the equation $\alpha = (100 \cdot \alpha)/(l \cdot c)$ and are reported as unit-less numbers where the concentration *c* is in g/l00 mL and the path length *l* is in decimeters. Mass spectrometry was performed at the mass spectrometry facility of the Department of Chemistry at The University of Utah on a double focusing high resolution mass spectrometer or at the mass spectrometry facility of the Department of Chemistry at the University of California, Riverside on an LCTOF mass spectrometer. The ratio of enantiomers (ee %) was determined by HPLC analysis using a Daicel Chiralcel OD-H 25 cm column. Compounds were named using ChemDraw 12.0.



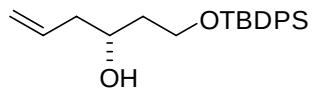
Preparation of 3-(*tert*-Butyl-diphenyl-silanyloxy)-propan-1-ol (2.43). To a stirring solution of 1,3-propandiol (24.9 g, 327 mmol, 3.0 equiv), *tert*-butyldiphenylsilyl chloride (30.0 g, 109 mmol, 1.0 equiv), 4-dimethylaminopyridine (133 mg, 1.09 mmol, 0.01 equiv) in CH_2Cl_2 (500 mL) in a 1000 mL rb flask under an atmosphere of N_2 at rt, was added triethylamine (16.5 g, 164 mmol, 1.5 equiv) dropwise via syringe. After 24 h at rt, the reaction was quenched by the addition of water (200 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 ml). The combined

organic phases were washed with brine (2 × 100 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product. Purification was accomplished by flash chromatography on a 6.5 × 32 cm silica gel column, eluting with 20% EtOAc/hexanes (4000 mL), collecting 25 mL fractions. The product containing fractions (75-152) were combined and concentrated under reduced pressure to give the product **2.43** as colorless crystals (32.6 g, 95% yield): MP = 41-42 °C; 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.67 (m, 4H), 7.47-7.38 (m, 6H), 3.86 (t, *J* = 5.9, Hz, 2H), 3.85 (ddd, *J* = 5.9, 5.4, 5.4 Hz, 2H), 2.35 (t, *J* = 5.4 Hz, 1H), 1.82 (dddd, *J* = 5.9, 5.9, 5.9, 5.4 Hz, 2H), 1.07 (s, 9H); 125 MHZ ^{13}C NMR ($CDCl_3$) δ 135.8, 133.5, 130.0, 128.0, 63.5, 62.1, 34.5, 27.0, 19.3. 125 MHz DEPT ($CDCl_3$) CH_3 δ 27.0; CH_2 δ 63.5, 62.1, 34.5; CH δ 135.8, 130.0, 128.0; CH_0 δ 133.5, 19.3.



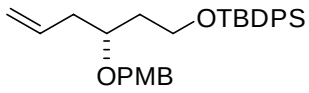
Preparation of 3-(*tert*-Butyl-diphenyl-silanyloxy)-propion-aldehyde (2.2). To a stirring solution of oxalyl chloride (10.6 g, 83.4 mmol, 1.5 equiv) in CH_2Cl_2 (625 mL) in a 1000 mL rb flask at -78 °C was added dimethyl sulfoxide (13.0 g, 166.8 mmol, 3.0 equiv) dropwise via syringe. After 1 h at -78°C, alcohol **2.43** (17.5 g, 55.6 mmol, 1.0 equiv) in CH_2Cl_2 (50 mL) was added dropwise via cannula. An additional CH_2Cl_2 rinse (25 mL) was used to transfer the remaining alcohol residue into the reaction flask. After 1 h at -78 °C, triethylamine (28.1 g, 278 mmol, 5.0 equiv) was added via syringe. After 2 h, the reaction was determined to be complete by TLC analysis and was then quenched by the addition of pH 7 buffer solution (100 mL). The phases were separated and the organic phase was washed with water (3 × 60 mL) and brine (3 × 60 mL), then dried over $MgSO_4$,

filtered, and concentrated under reduced pressure to give the crude product. The purification was accomplished by flash chromatography on a 6.5 × 30 cm silica gel column, eluting with 10% EtOAc/hexanes (3000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (44-97) were combined and concentrated under reduced pressure to give the aldehyde **2.2** (16.9 g, 97%) as white crystals: MP 40-42 ºC; 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.84 (t, *J* = 2.0 Hz, 1H), 7.69-7.65 (m, 4H), 7.47-7.38 (m, 6H), 4.04 (t, *J* = 5.9 Hz, 2H), 2.62 (td, *J* = 5.9, 2.0 Hz, 2H), 1.06 (s, 9H); 125 MHZ ^{13}C NMR ($CDCl_3$) δ 202.1, 135.8, 133.5, 130.0, 128.0, 58.5, 46.6, 27.0, 19.4. 125 MHz DEPT ($CDCl_3$) CH_3 δ 27.0; CH_2 δ 58.5, 46.6; CH δ 202.1, 135.8, 130.0, 128.0; CH_0 δ 133.5, 19.4.



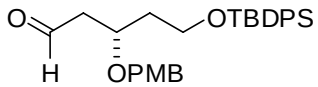
Preparation of (*R*)-1-(tert-butyldiphenylsilyloxy)hex-5-en-3-ol (2.44). A 250 mL rb flask was charged with a magnetic stir bar, oven dried 4Å molecular sieves (8.64 g) and CH_2Cl_2 (60 mL). To the stirring suspension were added (*R*)-BINOL (1.212 g, 4.234 mmol, 0.2 equiv) in one portion, a solution of Ti(O*i*-Pr)$_4$ (2.12 mL of 1.0 M, 2.117 mmol, 0.1 equiv) in CH_2Cl_2 via syringe, and a freshly prepared solution of trifluoroacetic acid (1.48 mL of 0.1 M, 0.148 mmol, 0.007 equiv) in CH_2Cl_2. The mixture was heated at reflux (~38ºC) for 1 h, and then allowed to cool to rt. A solution of aldehyde **2.2** (6.615 g, 21.16 mmol, 1.0 equiv) in CH_2Cl_2 (20 mL) was added via cannula. An additional CH_2Cl_2 (5 mL) rinse was used to transfer the remaining aldehyde residue into the reaction flask via cannula. The reaction mixture was stirred for another 0.5 h at rt before it was cooled to -78ºC. Allyltributyltin (10.51 g, 31.74 mmol, 1.5 equiv) was added to the reaction

mixture down the inside wall of the reaction flask via syringe. The reaction mixture was stirred for an additional 10 min at -78 ºC then transferred to a –20 ºC freezer. After 5 days, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (50 mL), then warmed to rt and stirred for 2 h. The molecular sieves were removed by filtration through a pad of celite®. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a red oil. Purification was accomplished by flash chromatography on a 6.5 × 27 cm silica gel column, eluting with 1500 mL hexanes and then 5% EtOAc/hexanes (3000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (83-140) was combined and concentrated under reduced pressure to give the product **2.44** (6.83 g, 91%) as a colorless oil: 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.76-7.68 (m, 4H), 7.49-7.38 (m, 6H), 5.88 (dddd, *J* = 17.1, 10.1, 7.1, 7.1 Hz, 1H), 5.17-5.11 (m, 2H), 4.00 (ddddd, *J* = 8.7, 6.1, 6.1, 3.0, 3.0 Hz, 1H), 3.94-3.84 (m, 2H), 3.28 (bs, 1H), 2.35-2.25 (m, 2H), 1.81-1.69 (m, 2H), 1.09 (s, 9H); 125 MHZ ^{13}C NMR ($CDCl_3$) δ 135.8, 135.8, 135.2, 133.3, 133.3, 130.0, 130.0, 128.0, 117.6, 71.1, 63.5, 42.2, 38.1, 27.0 19.3. 125 MHz DEPT ($CDCl_3$) CH_3 δ 27.0; CH_2 δ 117.6, 63.5, 42.2, 38.1; CH δ 135.8, 135.8, 135.2, 130.0, 130.0, 128.0, 71.1; CH_0 δ 133.3, 133.3, 19.3. Assay of enantiomeric excess: HPLC (5 % *i*-PrOH/hexanes, 0.45 mL/min); t_r (major) = 10.57 min, t_r (minor) = 9.48 min; 97% ee.

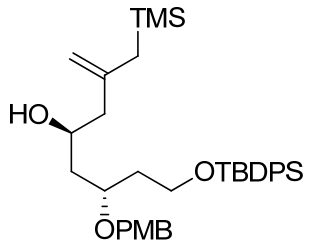


Preparation of (*R*)-tert-butyl(3-(4-methoxybenzyloxy)hex-5-enyloxy)diphenyl silane (2.45). To a solution of alcohol **2.44** (167 mg, 0.471 mmol, 1.0 equiv) in 3 mL

THF in a 25 mL rb flask under the atmosphere of N_2 was added a solution of *p*-methoxybenzyl bromide (473 mg, 2.35 mmol, 5.0 equiv) in 2 mL THF and triethylamine (713 mg, 7.05 mmol, 15 equiv) via syringe. The reaction mixture was cooled to -78ºC, and then a solution of 0.5 M potassium bis(trimethylsilyl)amide (2.82 mL, 1.41 mmol, 3.0 equiv) was added to the reaction dropwise via syringe. After 1 h at -78ºC, the reaction was warmed up to -15ºC and stirred for another 1.5 h. The reaction was quenched by addition of aqueous ammonium hydroxide (4.0 mL), and then the reaction was warmed up to rt and stirred overnight. The product was extract with Et_2O (10 mL × 3). The organic phase was combined, dried over Na_2SO_4 and concentrated under reduced pressure. The purification was accomplished by flash chromatography column on a 3.5 × 14 cm silica gel column, eluting with 3% EtOAc/hexanes (1000 mL), collecting 10 mL fractions. The product containing fractions (35-68) was combined and concentrated under reduced pressure to give the product **2.45** as a colorless oil (164 mg, 74% yield). 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.67 (m, 4H), 7.47-7.38 (m, 6H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 5.87 (dddd, *J* = 17.6, 10.3, 7.3, 7.3 HZ, 1H), 5.13-5.07 (m, 2H), 4.47 (ABq, *J* = 11.2, Δν = 54.5 Hz, 2H), 3.88-3.83 (m, 1H), 3.82 (s, 3H), 3.81-3.72 (m, 2H), 2.35 (t, *J* = 6.3 Hz, 2H), 1.83-1.77 (m, 2H), 1.08 (s, 9H); 125 MHZ ^{13}C NMR ($CDCl_3$) δ 159.3, 135.8, 135.1, 134.2, 134.2, 131.2, 129.8, 129.5, 127.8, 127.8, 117.1, 113.9, 75.3, 71.0, 60.7, 55.5, 38.7, 37.2, 27.1, 19.4; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.5, 27.1; CH_2 δ 117.1, 71.0, 60.7, 38.7, 37.2; CH δ 135.8, 135.1, 129.8, 129.5, 127.8, 127.8, 113.9, 75.3; CH_0 δ 159.3, 134.2, 134.2, 131.2, 19.4.

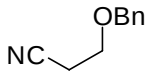


Preparation of (*S*)-5-(*tert*-butyldiphenylsilyloxy)-3-(4-methoxybenzyloxy) pen tanal (2.46).To a stirring solution of alkene **2.45** (2.766 g, 5.827 mmol, 1.0 equiv) in a mixture of 20% MeOH/CH_2Cl_2 (100 mL) in a 250 mL rb flask was added sodium bicarbonate (2.766 g) in one portion. The reaction mixture was cooled to -78 ºC, and then a steady stream of ozone was bubbled into the solution for 1 min, during which time the color changed to light grey. The mixture was then purged with a steady stream of oxygen. Triphenylphosphine (2.637 g, 11.65 mmol, 2.0 equiv) was added in one portion to the solution, which was then allowed to warm to rt over a period of 1 h. Solid $NaHCO_3$ was removed by filtration and the solution was concentrated under reduced pressure to give a yellow oil. Purification was accomplished by flash chromatography on a 5 × 18 cm silica gel column, eluting with 20% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (12-29) were combined and concentrated under reduced pressure to give the product **2.46** (2.494 g, 90%) as a colorless oil: 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.80 (t, *J* = 2.0 Hz, 1H), 7.73-7.69 (m, 4H), 7.51-7.41 (m, 6H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz,, 2H), 4.50 (s, 2H), 4.24 (dddd, *J* = 6.7, 6.7, 6.4, 5.7 Hz, 1H), 3.91-3.86 (m, 1H), 3.84 (s, 3H), 3.82-3.76 (m, 1H), 2.69 (ddd, *J* = 16.1, 7.1, 2.4 Hz, 1H), 2.63 (ddd, *J* = 16.4, 6.7, 1.7 Hz, 1H), 2.00-1.93 (m, 1H), 1.87-1.80 (m, 1H), 1.08(s, 9H). 125 MHZ ^{13}C NMR ($CDCl_3$) δ 201.8, 159.4, 135.7, 133.8, 133.7, 130.4, 129.9, 129.9, 129.6, 127.9, 114.0, 71.4, 71.3, 60.3, 55.4, 48.7, 37.3, 27.1, 19.3; 125 MHz DEPT ($CDCl_3$) CH3 δ 55.4, 27.1; CH2 δ 71.3, 60.3, 48.7, 37.3; CH δ 201.8, 135.8, 129.9, 129.9, 129.6, 127.9, 114.0, 71.4; CH_0 δ 159.4, 133.8, 133.7, 130.4, 19.3.

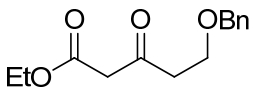


Preparation of (4*S*, 6*S*)-8-(tert-butyldiphenylsilyloxy)-6-(4-methoxybenzyloxy) -2-((trimethylsilyl)methyl)oct-1-en-4-ol (2.14). To a solution of aldehyde **2.46** (576 mg, 1.209 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL) in a 25 mL rb flask was added $MgBr_2 \cdot OEt_2$ (623 mg, 2.418 mmol, 2.0 equiv) in one portion at rt. After 5 min at rt, the reaction mixture was cooled to -78 ºC and stirred for 30 min. Stannane **2.1** (1.009 g, 2.418 mmol. 2.0 equiv) was added dropwise via syringe. After 5 h at -78 ºC, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 25 cm silica gel column, eluting with 8% acetone/hexanes (1000 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (35-61) was combined and concentrated under reduced pressure to give the product **2.14** (592 mg, 81%) as a colorless oil: 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.71-7.67 (m, 4H), 7.47-7.37 (m, 6H), 7.23 (d, *J* = 8.7Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.68 (dd, *J* = 1.0, 0.7 Hz, 1H), 4.66 (s, 1H), 4.48 (s, 2H), 4.04-3.96 (m, 2H), 3.85-3.79 (m, 1H), 3.81 (s, 3H), 3.76 (dt, *J* = 10.1, 6.0 Hz, 1H), 2.68 (d, *J* = 2.4 Hz, 1H), 2.12 (dd, *J* = 13.8, 8.4 Hz, 1H), 2.06 (dd, *J* = 13.8, 5.0 Hz, 1H), 1.94 (dq, *J* = 12.8, 6.0 Hz, 1H), 1.79 (dq, *J* = 13.8, 6.7 Hz, 1H), 1.72-1.60 (m, 2H), 1.55 (ABq, *J* = 13.4 Hz, Δν = 14.6 Hz, 2H), 1.08 (s, 9H), 0.04 (s, 9H);

125 MHZ ^{13}C NMR ($CDCl_3$) δ 159.4, 144.8, 135.8, 134.0, 134.0, 130.8, 129.8, 129.8, 127.9, 127.8, 127.8, 114.0, 110.2, 74.0, 71.6, 66.2, 60.7, 55.5, 47.0, 40.8, 37.3, 27.1, 26.9, 19.4, -1.1. 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 27.1, -1.1; CH_2 δ 110.2, 71.6, 60.7, 47.0, 40.8, 37.3, 27.1; CH δ 135.8, 129.8, 129.7, 127.9, 127.8, 114.0, 74.0, 66.2; CH_0 δ 159.4, 144.8, 134.0, 134.0, 130.8, 19.4.

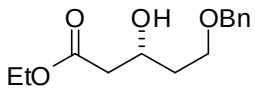


Preparation of 3-(benzyloxy)propanenitrile (2.48). To a stirring mixture of benzyl alcohol **2.47** (54.05 g, 500 mmol, 1.0 equiv) and 40% aqueous NaOH solution (5.0 mL) in a 250 mL rb flask at 0 ºC was added acrylonitrile (29.15 g, 550 mmol, 1.1 equiv) dropwise via syringe. The mixture was warmed to rt and stirred overnight. The solution was neutralized by the addition of 1.0 N HCl (50 ml), and diluted with CH_2Cl_2 (200 mL). The organic phase was separated, washed with 5% aqueous NaOH solution (25 mL) and brine (50 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the product **2.48** (80.4 g, quantitative) as a light yellow oil: 500 MHz ^1H NMR ($CDCl_3$) δ 7.40-7.30 (m, 5H), 4.60 (s, 2H), 3.69 (t, J = 6.4 Hz, 2H), 2.63 (t, J = 6.38 Hz, 2H); 125 MHZ ^{13}C NMR ($CDCl_3$) δ 137.4, 128.7, 128.2, 127.9, 118.0, 73.5, 64.7, 19.1.



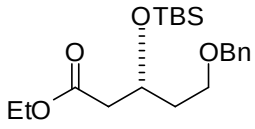
Preparation of ethyl 5-(benzyloxy)-3-oxopentanoate (2.41).[32] To a stirring solution of nitrile **2.48** (1.30 g, 8.06 mmol, 1.0 equiv) in THF (20 mL) in a three necked

50 mL rb flask equipped with a reflux condenser was added Zn/Cu couple (2.89 g, 44.3 mmol, 5.5 equiv). The mixture was heated to reflux, and then ethyl 2-bromoacetate (4.17 g, 25.0 mmol, 3.1 equiv) was added slowly by syringe pump over 2 h. The reaction mixture was then cooled to 0 ºC, and a solution of 3N HCl (20 mL) was added dropwise via syringe. The mixture was stirred at 0 ºC for 0.5 h, and then warmed to rt. The phases were separated and the aqueous phase was extracted with $CHCl_3$ (3 × 20 mL). The combined organic phases were washed with water (3 × 20 mL), saturated aqueous $NaHCO_3$ solution (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 4 × 19 cm silica gel column, eluting with 5% acetone/hexanes (1500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (23-59) were combined and concentrated under reduced pressure to give the product **2.41** (1.56 g, 78%) as a colorless oil: 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.35-7.25 (m, 5H), 4.50 (s, 2H), 4.17 (q, *J* = 7.3 Hz, 2H), 3.74 (t, *J* = 6.4 Hz, 2H), 3.47 (s, 2H), 2.82 (t, *J* = 6.3 Hz, 2H), 1.26 (t, *J* = 7.3 Hz, 3H); 125 MHZ ^{13}C NMR ($CDCl_3$) δ 201.5, 167.2, 138.1, 128.6, 127.9, 127.9, 73.4, 65.2, 61.5, 49.9, 43.3, 14.3. 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 14.3; CH_2 δ 73.4, 65.2, 61.5, 49.9, 43.3; CH δ 128.6, 127.9, 127.9; CH_0 δ 201.5, 167.2, 138.1.



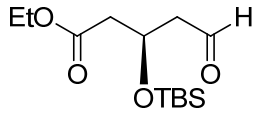
Preparation of (*R*)-ethyl 5-(benzyloxy)-3-hydroxypentanoate (2.49). A 250 mL Parr bomb was charged with a magnetic stir bar, ester **2.41** (26.10 g, 104.3 mmol, 1.0 equiv), degassed ethanol (91 mL) and [(*R*)-BINAP)]$RuCl_2$ (91.0 mg, 0.114 mmol, 0.0011 equiv) in the glove box. The gas inlet tube was attached to a hydrogen source and

hydrogen was introduced into the reaction vessel until the pressure gauge indicated 400 psi. The pressure was carefully released to 1 atm by opening the stop valve. This procedure was repeated for three times, and finally hydrogen is pressurized to 400 psi. The reaction solution was stirred at rt for 5 days, during which time the hydrogen cylinder was kept connected. After the main valve of the hydrogen cylinder was closed, excess hydrogen in the reaction tube was carefully bled off, and the apparatus was disassembled. The reaction mixture was passed through a short silica pad and washed with 20% EtOAc/hexanes (500 mL). The resulting solution was concentrated under reduced pressure to give the alcohol product **2.49** (24.80 g, 95%) as a colorless oil: R_f = 0.19 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = -12.1 (*c* = 1.12, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.32-7.22 (m, 5H), 4.47 (s, 2H), 4.20 (dddd, *J* = 6.4, 6.4, 6.4, 5.9 Hz, 1H), 4.12 (q, *J* = 6.8 Hz, 2H), 3.65 (ddd, *J* = 9.4, 6.4, 5.4 Hz, 1H), 3.60 (ddd, *J* = 9.4, 6.4, 5.4 Hz, 1H), 3.34 (bs, 1H), 2.44 (d, *J* = 6.4 Hz, 2H), 1.79-1.73 (m, 2H), 1.22 (t, *J* = 7.3 Hz, 3H); 125 MHZ ^{13}C NMR ($CDCl_3$) δ 172.6, 138.2, 128.6, 127.8, 127.8, 73.4, 68.0, 67.0, 60.7, 41.8, 36.2, 14.3; 125 MHz DEPT 13C NMR (CDCl3) CH_3 δ 14.3; CH_2 δ 73.4, 68.0, 60.7, 41.8, 36.2; CH δ 128.6, 127.8, 127.8, 67.0; CH_0 δ 172.6, 138.2; Chiral HPLC (15 % *i*-PrOH/hexanes; 0.50 mL/min); t_r (major) = 10.30 min, t_r (minor) = 11.24 min; 99% ee.



Preparation of (*R*)-ethyl 5-(benzyloxy)-3-(*tert*-butyldimethyl silyloxy) pent anoate (2.50). To a stirring solution of alcohol **2.49** (6.374 g, 25.26 mmol, 1.0 equiv) in DMF (135 mL, 0.19 M) in a 250 mL rb flask was added *tert*-butyldimethylsilyl chloride

(4.189 g, 27.70 mmol, 1.1 equiv) and imidazole (2.064 g, 30.32 mmol, 1.2 equiv) in one portion. After 12 h at rt, the reaction mixture was diluted with EtOAc (250 mL), then washed with water (100 mL), and brine (100 mL), and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. Purification was accomplished by flash chromatography on a 5.5 × 25 cm silica gel column, eluting with 10% EtOAc/hexanes (1500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (16-44) were combined and concentrated under reduced pressure to give the product **2.50** (8.781 g, 98%) as a colorless oil: R_f = 0.33 (10% EtOAc/hexanes); $[\alpha]_D^{20}$ = -5.5 (*c* = 1.28, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.32-7.20 (m, 5H), 4.42 (d, *J* = 6.4 Hz, 2H), 4.26 (dddd, *J* = 6.4, 5.9, 5.9, 5.9 Hz, 1H), 4.09-4.01 (m, 2H), 3.49 (t, *J* = 6.4 Hz, 2H), 2.42 (d, *J* = 6.4 Hz, 2H), 1.80 (dd, *J* = 6.4, 1.7 Hz, 1H), 1.77 (dd, *J* = 6.4, 2.0 Hz, 1H), 1.19 (t, *J* = 7.3 Hz, 3H), 0.80 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H). 125 MHZ ^{13}C NMR ($CDCl_3$) δ 171.7, 138.6, 128.5, 127.7, 127.7, 73.1, 67.1, 66.7, 60.5, 43.2, 37.6, 26.0, 18.2, 14.4. -4.5, -4.6. 125 MHz DEPT 13C NMR ($CDCl_3$) CH_3 δ 26.0, 14.4, -4.5, -4.6; CH_2 δ 73.1, 66.7, 60.5, 43.2, 37.6; CH δ 128.5, 127.7, 127.7, 67.1; CH0 δ 171.7, 138.6, 18.2.



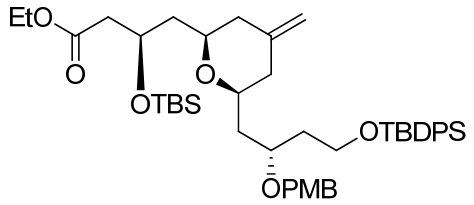
Preparation of (*R*)-ethyl 3-(*tert*-butyldimethylsilyloxy)-5-oxopentanoate (2.40)

To a stirring solution of ether **2.50** (1.86 g, 5.12 mmol, 1.0 equiv) in EtOAc (51 mL, 0.1 M) in a three-necked 100 mL rb flask was added 10 wt% Pd/C (0.5 g). The reaction flask was then equipped with a hydrogen balloon. After 2 days at rt, the reaction was

determined to be complete by TLC analysis. The reaction mixture was filtered over a pad of Celite®, and then concentrated under reduced pressure to give a colorless oil, which was used in the next step without purification.

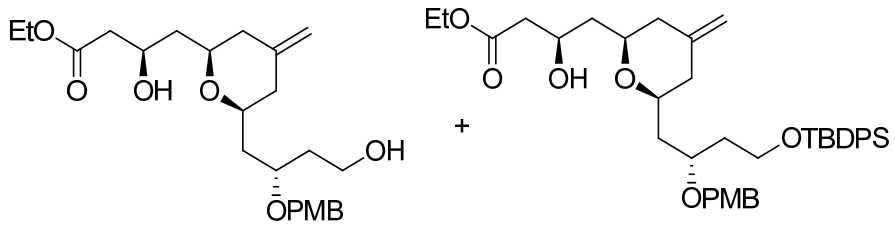
To a stirring solution of the aforementioned intermediate alcohol in CH_2Cl_2 (51 mL, 0.1 M) in a 100 mL rb flask was added diisopropylethylamine (4.63 g, 35.81 mmol, 7.0 equiv). The reaction mixture was cooled to -5 ºC, and then dimethyl sulfoxide (4.00 g, 20.46 mmol, 4.0 equiv) was added via syringe. After 5 min at -5 ºC, $SO_3 \cdot Py$ (3.26 g, 20.46 mmol, 4.0 equiv) was added in one portion. After 1 h at -5 ºC, the reaction mixture was poured into a 250 mL Erlenmeyer flask containing 25 mL of saturated aqueous $NaHCO_3$ solution. The reaction mixture was stirred at rt for 1 h, then the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined and washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 4 × 15 cm silica gel column, eluting with 10% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (12-20) were combined and concentrated under reduced pressure to provide the aldehyde **2.40** (1.35 g, 96% over 2 steps) as a yellow oil: R_f = 0.52 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = -9.9 (*c* = 1.15, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.80 (t, *J* = 2.0 Hz, 1H), 4.63 (dddd, *J* = 6.3, 6.3, 5.9, 5.9 Hz, 1H), 4.14 (m, 2H), 2.67 (ddd, *J* = 16.6, 5.4, 1.7 Hz, 1H), 2.62 (ddd, *J* = 16.6, 6.4, 2.4 Hz, 1H), 2.55 (dd, *J* = 15.1, 6.4 Hz, 1H), 2.55-2.50 (dd, *J* = 15.1, 6.4 Hz, 1H), 1.25 (t, *J* = 7.3 Hz, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 201.1, 170.9, 65.2, 60.8, 51.1, 42.8, 25.8, 18.1, 14.3, -4.6, -4.6; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 25.8, 14.3, -4.6, -4.6; CH_2 δ 60.8, 51.1, 42.8; CH δ

201.1, 65.2; CH_0 δ 170.9, 18.1; IR (neat) 2931, 2858, 2728, 1734, 1473, 1377, 1317, 1257, 1173, 1095, 1006, 940, 838, 813, 778, 681 cm^{-1}; LRMS (EI) Calcd for $C_{13}H_{27}O_4Si$ (M+H): 275.2, Found: 275.2; HRMS (ESI/TOF) calcd for $C_{13}H_{26}NaO_4Si$ (M+Na) 297.1493, found 297.1488.



Preparation of (*R*)-ethyl 3-(tert-butyldimethyl silyloxy)-4-((2*R*,6*S*)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy) butyl)-4-methylenetetra hydro-2H-pyran-2-yl)butanoate (2.39). To a stirring solution of aldehyde **2.40** (256 mg, 0.933 mmol, 1.0 equiv) and hydroxyallylsilane **2.14** (621 mg, 1.03 mmol, 1.1 equiv) in Et_2O (10 mL, 0.1M) in a 25 mL rb flask at -78 ºC was added trimethylsilyl triflate (249 mg, 1.12 mmol, 1.2 equiv) dropwise via syringe. After 1 h at -78 ºC, the reaction mixture was quenched by the addition of diisopropylethylamine (0.2 mL) via syringe, followed by the addition of saturated aqueous $NaHCO_3$ solution (2 mL). The mixture was warmed to rt, then the phases were separated, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 21 cm silica gel column, eluting with 5% EtOAc/hexanes (2500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (24-50) were combined and concentrated under reduced pressure to provide the pyran **2.39** (750 mg, 96%) as a colorless oil: R_f = 0.65 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +2.2 (*c* = 1.11, $CHCl_3$); 500 MHz

^{1}H NMR ($CDCl_3$) δ 7.74-7.71 (m, 4H), 7.47-7.39 (m, 6H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.75 (s, 1H), 4.73 (s, 1H), 4.45 (ABq, *J* = 10.8, Δν = 24.1 Hz, 2H), 4.43-4.38 (m, 1H), 4.12 (dq, *J* = 10.8, 7.3 Hz, 1H), 4.06 (dq, *J* = 10.7, 7.3 Hz, 1H), 3.92 (dddd, *J* = 6.3, 6.3, 5.9, 5.9 Hz, 1H), 3.88-3.76 (m, 5H), 3.58-3.52 (m, 1H), 3.50-3.44 (m, 1H), 2.58-2.50 (m, 2H), 2.26 (d, *J* = 13.2 Hz, 1H), 2.19 (d, *J* = 12.7 Hz, 1H), 1.98 (dd, *J* = 22.5, 11.7Hz, 2H), 1.92-1.83 (m, 3H), 1.72-1.66 (m, 3H), 1.21 (t, *J* = 7.3 Hz, 3H), 1.10 (s, 9H), 0.90 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.8, 159.2, 144.8, 135.8, 134.1 (×2), 131.3, 129.8, 129.5, 127.8 (×2), 113.9, 108.7, 75.1, 75.0, 73.0, 71.8, 66.9, 60.8, 60.4, 55.4, 44.1, 42.8, 42.5, 41.3 (×2), 37.9, 27.1, 26.0, 19.4, 18.1, 14.3, -4.2, -4.6; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.4, 27.1, 26.0, 14.3, -4.2, -4.6; CH_2 δ 108.7, 71.8, 60.8, 60.4, 44.1, 43.8, 42.8, 42.5, 41.3 (×2), 37.9; CH δ 135.8, 129.8, 129.5, 127.8 (×2), 113.9, 75.1, 75.0, 73.0, 66.9; CH_0 δ 171.8, 159.2, 144.8, 134.1 (×2), 131.3, 19.4, 18.1; IR (neat) 3072, 2933, 2857, 1737, 1652, 1613, 1588, 1514, 1472, 1428, 1390, 1302, 1249, 1174, 1111, 1039, 940, 837, 777, 738, 702, 615, 505 cm^{-1}; LRMS(EI) Calcd for $C_{46}H_{69}O_7Si_2$ (M+H): 789.5, Found: 789.2; HRMS (ESI/TOF) calcd for $C_{46}H_{68}NaO_7Si_2$ (M+Na) 811.4396, found 811.4389.



Preparation of (*R*)-ethyl-4-((2*R*,6*S*)-6-((*S*)-4-(hydroxy)-2-(4-methoxy benzyl oxy) butyl)-4-methylenetetra hydro-2H-pyran-2-yl)-3-hydroxy butanoate and (*R*)-ethyl 4-((2*R*,6*S*)-6-((*S*)-4-(*tert*-butyldiphenyl silyloxy)-2-(4-methoxybenzyloxy)butyl)-

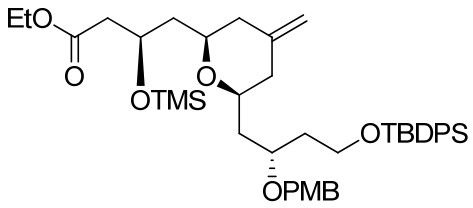
4-methylene tetrahydro-2H-pyran-2-yl)-3-hydroxy butanoate (2.51 and 2.52). To a stirring solution of silyl ether **2.39** (77.2 mg, 0.098 mmol, 1.0 equiv) in a mixture of 3:2 benzene/MeOH (6.0 mL, 0.016 M) in a 25 mL rb flask was added *p*-toluenesulfonic acid (37.2 mg, 0.20 mmol, 2.0 equiv) in one portion. After 5 h at rt, the reaction mixture was quenched by the addition of triethylamine (0.2 mL), and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 8 cm silica gel column, eluting with 20% EtOAc/hexanes (500 mL) and 35% EtOAc/hexanes (500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (11-23) were combined and concentrated under reduced pressure to give the mono-deprotected product **2.51** (39.0 mg, 59%) as a colorless oil: R_f = 0.31 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +5.6 (*c* = 2.36, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.66 (m, 4H), 7.46-7.38 (m, 6H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 4.72 (d, *J* = 1.7 Hz, 1H), 4.70 (d, *J* = 1.7 Hz, 1H), 4.40 (ABq, *J* = 11.1 Hz, Δν = 40.4 Hz, 2H), 4.30-4.24 (m, 1H), 4.18-4.12 (m, 2H), 3.83-3.75 (m, 7H), 3.57-3.50 (m, 2H), 2.55 (dd, *J* = 15.8, 7.7 Hz, 1H), 2.45 (dd, *J* =15.8, 5.4 Hz, 1H), 2.25 (d, *J* = 13.1 Hz, 1H), 2.17 (d, *J* = 13.1 Hz, 1H), 2.00 (t, *J* = 12.1 Hz, 1H), 1.94 (t, *J* = 11.4 Hz, 1H), 1.86-1.64 (m, 6H), 1.25 (t, *J* = 7.4 Hz, 3H), 1.08 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.1, 159.3, 143.9, 135.8, 134.0 (×2), 131.0, 129.8 (×2), 129.7, 127.8 (×2), 114.0, 109.2, 78.3, 75.4, 72.7, 71.5, 67.8, 60.7, 60.5, 55.4, 42.5, 42.1, 41.9, 41.0 (×2), 37.5, 27.1, 19.3, 14.4; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.4, 27.1, 14.4; CH_2 δ 109.2, 71.6, 60.7, 60.5, 42.5, 42.1, 41.9, 41.0 (×2), 37.5; CH δ 135.8, 129.8 (×2), 129.7, 127.9, 114.0, 78.4, 75.5, 72.8, 67.8; CH_0 δ 172.1, 159.3, 143.9, 134.0 (×2), 131.0, 19.3; IR (neat) 3496, 3072, 2937, 1734, 1653, 1613, 1588, 1514, 1472, 1428, 1372, 1303, 1248, 1180, 1111, 1037, 891, 823, 738, 703, 615, 505 cm^{-1};

LRMS (EI) calcd for $C_{40}H_{55}O_7Si$ (M+H) 675.4, found 675.2; HRMS (ESI/TOF) calcd for $C_{40}H_{54}NaO_7Si$ (M+Na) 697.3531, found 697.3533.

The product containing fractions (56-70) were combined and concentrated under reduced pressure to provide the di-deprotected product **2.52** (15 mg, 34%) as a colorless oil: R_f = 0.38 (EtOAc); $[\alpha]_D^{20}$ = +3.0 (*c* = 0.570, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.27 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.75 (s, 2H), 4.49 (ABq, *J* = 11.2, Δν = 36.4 Hz, 2H), 4.27-4.21 (m, 1H), 4.16 (q, *J* = 7.3 Hz, 2H), 3.83-3.75 (m, 2H), 3.82 (s, 3H), 3.74-3.67 (m, 1H), 3.55-3.47 (m, 2H), 3.38 (bs, 1H), 2.52 (dd, *J* = 15.6, 7.8 Hz, 1H), 2.44 (dd, *J* = 15.6, 5.4 Hz, 1H), 2.27 (bs, 1H), 2.25-2.16 (m, 2H), 2.00 (d, *J* = 12.2 Hz, 1H),1.95 (q, *J* = 11.7 Hz, 1H), 1.92-1.85 (m, 1H), 1.79-1.64 (m, 5H), 1.26 (t, *J* = 7.3 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.1, 159.4, 143.7, 130.6, 129.9, 114.1, 109.4, 78.4, 75.8, 74.5, 71.6, 67.8, 60.8, 60.1, 55.5, 42.5, 42.1, 41.4, 41.1, 41.0, 36.6, 14.4; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5 14.4; CH_2 δ 109.5, 71.6, 60.8, 60.1, 42.5, 42.1, 41.4, 41.1, 41.0, 36.6; CH δ 129.9, 114.1, 78.5, 75.8, 74.5, 67.8; CH_0 δ 172.1, 159.4, 143.7, 130.6; IR (neat) 3450, 2940, 1733, 1653, 1613, 1514, 1372, 1302, 1248, 1175, 1035, 893, 822, 705, 542 cm^{-1}; LRMS (EI) calcd for $C_{24}H_{37}O_7$ (M+H) 437.3, Found 437.2; HRMS (ESI/TOF) calcd for $C_{24}H_{36}NaO_7$ (M+Na) 459.2353, found 459.2349.

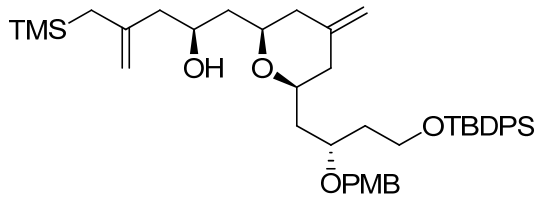
To a stirring solution of diol **2.51** (140 mg, 0.32 mmol, 1.0 equiv) in CH_2Cl_2 (5.0 mL, 0.064 M) in a 15 mL rb flask were added 4-dimethylaminopyridine (catalytic amount), *tert*-butyldiphenylsilyl chloride (132 mg, 0.481 mmol, 1.5 equiv) and triethylamine (48.7 mg, 0.481 mmol, 1.5 equiv) via syringe. After 12 h at rt, the reaction mixture was quenched by the addition of water (5.0 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic phases were

combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 15 cm silica gel column, eluting with 20% EtOAc/hexanes (500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (9-12) were combined and concentrated under reduced pressure to provide the alcohol **2.52** (210 mg, 97%) as a colorless oil. The overall yield from **2.39** to **2.52** is 92%.



Preparation of (*R*)-ethyl 4-((2*R*,6*S*)-6-((*S*)-4-(*tert*-butyldiphenyl silyloxy)-2-(4-methoxybenzyloxy)butyl)-4-methylenetetrahydro-2H-pyran-2-yl)-3-(trimethyl silyloxy) butanoate (2.53). To a stirring solution of alcohol **2.52** (751 mg, 1.11 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL, 0.03 M) in a 100 mL rb flask were added trimethylsilyl chloride (363 mg, 3.34 mmol, 3.0 equiv), and triethylamine (676 mg, 6.68 mmol, 6.0 equiv) dropwise via syringe. After 12 h at rt, the reaction mixture was quenched by the addition of water (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 4.5 × 17 cm silica gel column, eluting with 10% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (15-21) were combined and concentrated under reduced pressure to provide the silyl ether **2.53** (823 mg, 99%) as a colorless oil: R_f = 0.60 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ =

+5.9 (*c* =1.07, $CHCl_3$); 500 MHz ^1H NMR ($CDCl_3$) δ 7.75-7.70 (m, 4H), 7.50-7.40 (m, 6H), 7.24-7.20 (m, 2H), 6.90-6.86 (m, 2H), 4.76 (d, *J* =1.0 Hz, 1H), 4.74 (s, 1H), 4.47 (ABq, *J* = 10.7 Hz, Δν = 27.2 Hz, 2H), 4.43-4.39 (m, 1H), 4.18-4.06 (m, 2H), 3.94 (m, 1H), 3.88-3.79 (m, 5H), 3.60-3.52 (m, 1H), 3.48-3.40 (m, 1H), 2.54 (d, *J* = 1.0 Hz, 1H), 2.53 (s, 1H), 2.30 (d, *J* = 12.7 Hz, 1H), 2.22 (d, *J* = 13.2 Hz, 1H), 2.01 (d, *J* = 13.2 Hz, 1H), 1.95 (d, *J* = 12.2 Hz, 1H), 1.94-1.84 (m, 3H), 1.72-1.66 (m, 3H), 1.22 (t, *J* = 7.3 Hz, 3H), 1.10 (s, 9H), 0.16 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.7, 159.2, 144.7, 135.8 (×2), 134.1, 134.0, 131.2, 129.7, 129.5, 127.8, 113.9, 108.7, 75.1 (×2), 72.8, 71.7, 66.8, 60.7, 60.4, 55.4, 44.2, 43.0, 42.4, 41.3, 41.1, 37.8, 27.1, 19.3, 14.4, 0.5; 125 MHZ DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.4, 27.1, 14.4, 0.5; CH_2: 108.7, 71.7, 60.7, 60.4, 44.2, 43.0, 42.4, 41.3, 41.1, 37.8; CH: 135.8 (×2), 129.7, 129.5, 127.8, 113.9, 75.1 (×2), 72.8, 66.8; CH_0: 171.7, 159.2, 144.7, 134.1, 134.0, 131.2, 19.3; IR (neat) 3072, 2940, 1737, 1653, 1613, 1588, 1514, 1473, 1428, 1376, 1302, 1250, 1177, 1111, 1038, 842, 742, 703, 615 cm^{-1}; LRMS (EI) Calcd for $C_{43}H_{63}O_7Si_2$ (M+H) 747.4, Found 747.2; HRMS (ESI/TOF) calcd for $C_{43}H_{62}NaO_7Si_2$ (M+Na) 769.3926, found 769.3931.



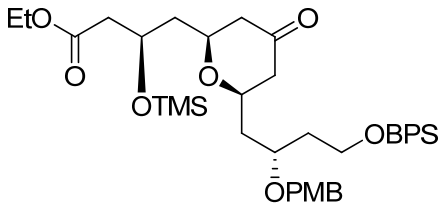
Preparation of (*S*)-1-((2*R*,6*S*)-6-((*S*)-4-(*tert*-butyldiphenyl silyloxy)-2-(4-meth oxybenzyloxy) butyl)-4-methylenetetrahydro-2H-pyran-2-yl)-4-((trimethylsilyl)meth yl) pent-4-en-2-ol (2.38). A 10 mL rb flask was charged with powdered $CeCl_3 \cdot 7H_2O$ (773 mg, 2.07 mmol, 10.0 equiv) and heated to 170 ºC under 1 mmg Hg vacuum. After

16 h at 170 ºC , the dry $CeCl_3$ was cooled to rt, and the flask was flushed with N_2. THF (2.0 mL) was added via syringe, and the mixture was stirred at rt for 2 h.

Meanwhile, to a 25 mL three-necked rb flask equipped with a condenser and a magnetic stir bar, were added magnesium turnings (124 mg, 5.0 mmol), and a crystal of iodine. The flask was heated with a heat gun for 5 min while stirring. THF (5.0 mL) was added into the reaction flask via syringe, and the reaction mixture was heated with a heat gun to reflux. Chloromethyl trimethylsilane (0.613 g, 5.0 mmol) was then added dropwise via syringe. The mixture was stirred at rt for 1.5 h to afford a 1.0 M solution of $TMSCH_2MgCl$.

The reaction flask containing $CeCl_3$ was cooled to -78 ºC, then a solution of $TMSCH_2MgCl$ (2.07 mL, 2.07 mmol, 10.0 equiv) was added dropwise via syringe. After 1 h at -78 ºC, a solution of ester **2.53** (155 mg, 0.207 mmol, 1.0 equiv) in THF (1.8 mL) was added via cannula. Additional THF (0.2 mL) was used to transfer the remaining ester residue into the reaction mixture. The resulting mixture was allowed to warm to rt and stirred overnight. The reaction was recooled to -78 ºC, and then a 1N HCl solution (4.0 mL) was added dropwise via syringe. The mixture was warmed to rt and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL). The organic phases were combined, and washed with saturated aqueous $NaHCO_3$ solution (10 mL), and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 14 cm silica gel column, eluting with 10% EtOAc/hexanes (1000 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (48-100) were combined and concentrated under reduced pressure to provide the hydroxyallylsilane **2.38** (120 mg, 81%) as a colorless oil: R_f = 0.55 (20%

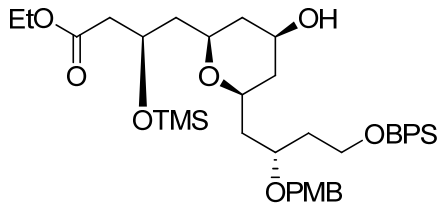
EtOAc/hexanes); $[\alpha]_D^{20}$ = +2.5 (*c* = 0.51, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-7.66 (m, 4H), 7.46-7.36 (m, 6H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.72 (d, *J* = 1.7 Hz, 1H), 4.70 (d, J = 1.7 Hz, 1H), 4.67-4.63 (m, 2H), 4.41 (ABq, *J* = 10.7 Hz, Δν = 30.4 Hz, 2H), 3.97 (m, 1H), 3.82-3.73 (m, 6H), 3.59-3.48 (m, 3H), 2.26-2.16 (m, 3H), 2.09-2.04 (dd, *J* =13.8, 6.4 Hz, 1H), 2.00 (t, *J* = 12.1 Hz, 1H), 1.94 (t, *J* = 12.1 Hz, 1H), 1.80 (q, *J* = 6.4 Hz, 2H), 1.73-1.60 (m, 4H), 1.56 (s, 2H), 1.07 (s, 9H), 0.03 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 159.3, 144.7, 144.2, 135.8, 134.1 (×2), 131.1, 129.8 (×2), 129.7, 127.9, 114.0, 110.0, 109.1, 79.3, 75.6, 72.9, 71.6, 69.7, 60.6, 55.5, 46.6, 42.6, 42.0, 41.2, 41.1, 37.6, 27.2, 27.1, 19.4, -1.1; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 27.1, -1.1; CH_2 δ 110.0, 109.1, 71.6, 60.6, 46.6, 42.6, 42.0, 41.2, 41.1, 37.6, 27.2; CH δ 135.8, 129.8 (×2), 129.7, 127.9, 114.0, 79.3, 75.6, 72.9, 69.7; CH_0 δ 159.3, 144.7, 144.2, 134.1 (×2), 131.1, 19.4; IR (neat) 3504, 3072, 2940, 1653, 1613, 1588, 1514, 1472, 1428, 1361, 1303, 1248, 1116, 1038, 849, 738, 702, 615, 505 cm^{-1}; LRMS (EI) Calcd for $C_{43}H_{63}O_5Si_2$ (M+H) 715.4, Found 715.2; HRMS (ESI/TOF) calcd for $C_{43}H_{62}NaO_5Si_2$ (M+Na) 737.4028, found 737.4032.



Preparation of (*R*)-ethyl 4-((2*S*,6*R*)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxy benzyloxy)butyl)-4-oxotetrahydro-2H-pyran-2-yl)-3-(trimethylsilyloxy) but anoate (2.54). To a stirring solution of alkene **2.53** (109.0 mg, 0.146 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL, 0.0058 M) in a 50 ml rb flask was added $NaHCO_3$ (109.0 mg). The

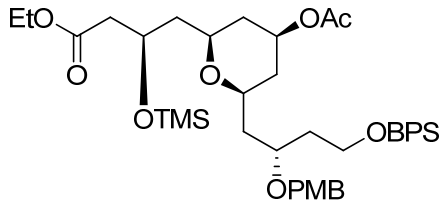
mixture was cooled to -78 ºC, and then a steady stream of ozone was bubbled through the solution for 1 min, during which time the solution developed a light grey color. The solution was then purged with a steady stream of oxygen until the grey color disappeared. Triphenylphosphine (115 mg, 0.438 mmol, 3.0 equiv) was added in one portion, and the reaction mixture was allowed to warm to rt and stir overnight. The solid $NaHCO_3$ was removed by filtration and the filtrate was concentrated under reduced pressure to give a yellow oil. Purification was accomplished by flash chromatography on a 2 × 17 cm silica gel column, eluting with 20% EtOAc/hexanes (500 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (6-10) were combined and concentrated under reduced pressure to give the product **2.54** (98.8 mg, 91% yield) as a colorless oil: R_f = 0.27 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +13.7 (*c* = 1.65, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) 7.69 (dd, *J* = 3.0, 1.4 Hz, 2H), 7.67 (dd, *J* = 3.0, 1.4 Hz, 2H), 7.45-7.36 (m, 6H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.47 (d, *J* = 11.1 Hz, 1H), 4.38-4.32 (m, 1H), 4.36 (d, *J* = 10.7 Hz, 1H), 4.11 (dddd, *J* = 10.7, 7.1, 7.1, 7.1 Hz, 1H), 4.05 (dddd, *J* = 10.7, 7.1, 7.1, 7.1 Hz, 1H), 3.91 (dddd, *J* = 9.1, 5.7, 5.7, 3.0 Hz, 1H), 3.83 (dddd, *J* = 9.1, 9.1, 2.7, 2.7 Hz, 1H), 3.84-3.78 (m, 5H), 3.76-3.70 (m, 2H), 2.53 (dd, *J* = 14.8, 7.7 Hz, 1H), 2.48 (dd, *J* = 14.8, 7.7 Hz, 1H), 2.40 (ddd, *J* = 14.4, 2.0, 2.0 Hz, 1H), 2.33 (ddd, *J* = 14.4, 2.0, 2.0 Hz, 1H), 2.25 (dd, *J* = 14.1, 11.8 Hz, 1H), 2.20 (dd, *J* = 14.1, 11.8 Hz, 1H), 1.96-1.86 (m, 2H), 1.84-1.73 (m, 2H), 1.72-1.62 (m, 2H), 1.20 (t, *J* = 7.4 Hz, 3H), 1.06 (s, 9H), 0.10 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 207.1, 171.5, 159.3, 135.8, 135.8, 134.0, 134.0, 131.0, 129.8, 129.5, 127.9, 127.9, 114.0, 73.8, 73.6, 72.7, 71.6, 66.4, 60.6, 60.5, 55.5, 48.3, 48.1, 44.0, 42.8, 42.6, 37.4, 27.1, 19.4, 14.4, 0.5; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 27.1, 14.4, 0.5; CH_2 δ 71.6, 60.6, 60.6, 48.3, 48.1, 44.0,

42.8, 42.6, 37.4; CH δ 135.8, 129.8, 129.5, 129.5, 127.9, 73.8, 73.6, 72.7, 66.4; CH0 δ 207.1, 171.5, 159.3, 19.3; IR (neat) 2956, 1732, 1612, 1513, 1428, 1377, 1302, 1249, 1173, 1111, 1037, 842, 742, 703, 614, 542 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{42}H_{60}O_8NaSi_2$ (M+Na) 771.3719, found 771.3715.



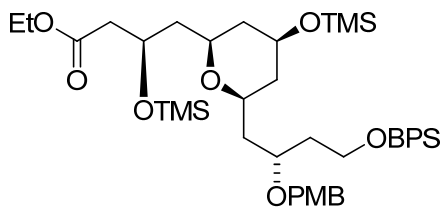
Preparation of (*R*)-ethyl 4-((2*R*,4*S*,6*S*)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxy benzyloxy)butyl)-4-hydroxytetrahydro-2H-pyran-2-yl)-3-(trimethylsilyl oxy) butanoate (2.55). To a solution of ketone **2.54** (59.0 mg, 0.0788 mmol, 1.0 equiv) in MeOH (5.0 mL, 0.015M) in a 15 mL rb flask at 0 ºC was added $NaBH_4$ (6.0 mg, 0.158 mmol, 2.0 equiv) in one portion. After 30 min at 0 ºC, the mixture was quenched by the addition of acetone (0.1 mL), and then concentrated under reduced pressure. Purification was accomplished by flash chromatography column on a 3 × 12 cm silica gel column, eluting with 40% EtOAc/hexanes (500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (6-10) were combined and concentrated under reduced pressure to give the alcohol product **2.55** (55.6 mg, 94%) as a colorless oil: R_f = 0.40 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = +16 (*c* = 0.29, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-7.66 (m, 4H), 7.46-7.37 (m, 6H), 7.17 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.38 (d, *J* = 11.1 Hz, 1H), 4.40-4.32 (m, 1H), 4.10 (dddd, *J* = 10.7, 7.1, 7.1, 7.1 Hz, 1H), 4.05 (dddd, *J* = 10.7, 7.1, 7.1, 7.1 Hz, 1H), 3.91-3.86 (m, 1H), 3.82-3.74 (m, 7H), 3.56-3.50 (m, 1H), 3.46-3.39 (m, 1H), 2.50 (d, *J* = 5.5 Hz, 1H), 2.49 (d, *J* = 3.0

Hz, 1H), 1.97 (ddd, *J* = 12.4, 4.4, 2.4 Hz, 1H), 1.90-1.76 (m, 4H), 1.68-1.45 (m, 5H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.06 (s, 9H), 0.12 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.8, 159.3, 135.8, 135.8, 134.1, 134.1, 131.2, 129.8, 129.5, 127.9, 127.9, 114.0, 72.9, 72.1, 72.1, 71.7, 68.3, 66.8, 60.7, 60.5, 55.5, 43.9, 42.9, 42.3, 41.8, 41.5, 37.8, 27.1, 19.4, 14.4, 0.5; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 27.1, 14.4, 0.5; CH_2 δ 71.7, 60.7, 60.5, 43.9, 42.9, 42.3, 41.8, 41.5, 37.8; CH δ 135.8, 135.8, 129.8, 129.5, 127.9, 127.9, 114.0, 72.9, 72.1, 68.4, 66.8; CH0 δ 171.8, 159.3, 134.1, 134.1, 131.2, 19.4; IR (neat) 3440, 2940, 1735, 1612, 1513, 1428, 1376, 1250, 1175, 1109, 1037, 741, 704, 613, 536 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{42}H_{62}O_8Na$ (M+Na) 773.3881, found 773.3886.



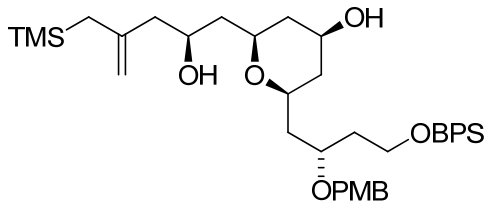
Preparation of (*R*)-ethyl 4-((2*R*,4*S*,6*R*)-4-acetoxy-6-((*S*)-4-(*tert*-butyldiphenyl silyloxy) -2-(4-methoxy benzyloxy) butyl) tetrahydro-2H-pyran-2-yl)-3-(trimethyl silyloxy) butanoate (2.58). To a stirring solution of alcohol **2.55** (25.0 mg, 0.0333 mmol, 1.0 equiv) in CH_2Cl_2 (3.3 mL, 0.01 M) in a 15 mL rb flask at rt were added 4-dimethylaminopyridine (4.1 mg, 0.0333 mmol, 1.0 equiv), pyridine (105.4 mg, 1.332 mmol, 40.0 equiv), and acetic anhydride (68.0 mg, 0.666 mmol, 20.0 equiv) via syringe. The solution was stirred at rt overnight, and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished by

flash chromatography on a 2 × 12 cm silica gel column, eluting with 50% EtOAc/hexane (250 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (2-4) were combined and concentrated under reduced pressure to give the product **2.58** (12.1 mg, 46% yield) as colorless oil: R_f = 0.34 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = + 9 (*c* = 0.27, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-7.66 (m, 4H), 7.45-7.36 (m, 6H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.88 (dddd, *J* = 11.2, 11.2, 4.9, 4.9 Hz, 1H), 4.45 (d, *J* = 10.7 Hz, 1H), 4.36 (d, *J* = 11.2 Hz, 1H), 4.33 (dddd, *J* = 6.3, 6.3, 6.3, 6.3 Hz, 1H), 4.10 (dddd, *J* = 10.7, 7.3, 7.3, 7.3 Hz, 1H), 4.05 (dddd, *J* = 10.7, 7.3, 7.3, 7.3 Hz, 1H), 3.86 (m, 1H), 3.82-3.74 (m, 5H), 3.62-3.56 (m, 1H), 3.52-3.46 (m, 1H), 2.48 (d, *J* = 2.9 Hz, 1H), 2.47 (s, 1H), 2.05 (s, 3H), 2.03-2.00 (m, 1H), 1.92-1.76 (m, 5H), 1.70-1.56 (m, 4H), 1.20 (t, *J* = 7.3 Hz, 3H), 1.07 (s, 9H), 0.12 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.7, 170.6, 159.3, 135.8, 134.0, 134.0, 131.1, 129.8, 129.5, 127.8, 114.0, 72.8, 72.1, 72.0, 71.8, 70.6, 66.7, 60.7, 60.5, 55.5, 43.9, 42.9, 42.2, 37.8, 37.7, 37.6, 27.1, 21.5, 19.4, 14.4, 0.5; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 27.1, 21.5, 14.4, 0.5; CH_2 δ 71.8, 60.7, 60.5, 43.9, 42.9, 42.2, 37.8, 37.7, 37.6; CH δ 135.8, 129.8, 129.5, 127.8, 114.0, 72.8, 72.1, 72.0, 70.6, 66.7; CH0 δ 171.7, 170.6, 159.3, 134.0, 134.0, 131.1, 19.4; IR (neat) 2953, 2859, 1738, 1612, 1513, 1428, 1365, 1247, 1175, 1109, 1033, 842, 741, 704, 612, 536 cm^{-1}; HRMS (ESI/TOF) calcd $C_{44}H_{64}O_9NaSi_2$ for (M+Na) 815.3987, found 815.4017.



Preparation of (*R*)-ethyl 4-((2*R*,4*S*,6*R*)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxy benzyloxy)butyl)-4-(trimethylsilyloxy) tetrahydro-2H-pyran-2-yl)-3-(trimethylsilyloxy) butanoate (2.56). To a solution of alcohol **2.55** (83.1 mg, 0.111 mmol, 1.0 equiv) in CH_2Cl_2 (11 mL, 0.01 M) in a 25 mL rb flask were added chlorotrimethylsilane (60.3 mg, 0.555 mmol, 5.0 equiv) and triethylamine (112.3 mg, 1.11 mmol, 10.0 equiv) dropwise via syringe. After 12 h at rt, the reaction mixture was quenched by the addition of water (5.0 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3.5 × 13 cm silica gel column, eluting with 10% EtOAc/hexanes (500 mL), collecting 18 mm × 150 mm test tube fractions. The product containing fractions (5-9) were combined and concentrated under reduced pressure to give the product **2.56** (87.6 mg, 96% yield) as a colorless oil: R_f = 0.52 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +12.5 (*c* = 2.71, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.69 (ddd, *J* = 4.4, 1.4, 1.4 Hz, 2H), 7.67 (dd, *J* = 4.0, 1.7 Hz, 2H), 7.45-7.35 (m, 6H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.45 (d, *J* = 11.1 Hz, 1H), 4.37 (d, *J* = 11.1 Hz, 1H), 4.37-4.30 (m, 1H), 4.10 (dddd, *J* = 10.7, 7.1, 7.1, 7.1 Hz, 1H), 4.05 (dddd, *J* = 10.7, 7.1, 7.1, 7.1 Hz, 1H), 3.90-3.84 (m, 1H), 3.80 (s, 3H), 3.80-3.71 (m, 3H), 3.56-3.50 (m, 1H), 3.45-3.38 (m, 1H), 2.50 (d, *J* = 4.7 Hz, 1H), 2.48 (d, *J* = 2.7 Hz, 1H), 1.86-1.72 (m, 5H), 1.66-1.54 (m, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.05 (s, 9H), 0.13 (s, 9H), 0.11 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.8, 159.3, 135.8, 135.8, 134.1, 134.1, 129.8, 129.6, 127.9, 114.0, 72.9, 72.2, 72.1, 71.8, 68.8, 66.8, 60.7, 60.5, 55.5, 44.0, 43.1, 42.3, 42.3, 41.9, 37.7, 27.1, 19.4, 14.4, 0.5, 0.5; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 27.1,

14.4, 0.5, 0.5; CH_2 δ 71.8, 60.7, 60.5, 44.0, 43.1, 42.3, 42.3, 41.9, 37.7; CH δ 135.8, 129.8, 129.6, 127.9, 114.0, 72.9, 72.2, 72.1, 68.8, 66.8; CH0 δ 171.8, 159.3, 135.8, 134.1, 134.1, 19.4; IR (neat) 3071, 2952, 2859, 1613, 1588, 1467, 1428, 1377, 1302, 1250, 1175, 1110, 744 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{45}H_{70}O_8NaSi_3$ (M+Na) 845.4271, found 845.4263.

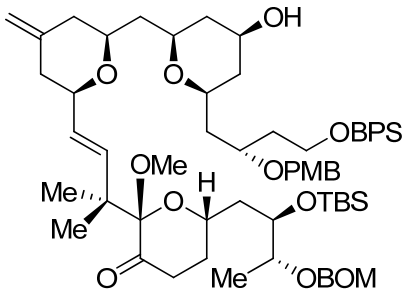


Preparation of (2*S*,4*R*,6*S*)-2-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxy benzyloxy) butyl)-6-((*S*)-2-hydroxy-4-((trimethylsilyl) methyl)pent-4-enyl)tetrahydro-2H-pyran-4-ol (2.57). Powdered $CeCl_3 \cdot 7H_2O$ (757.0 mg, 2.03 mmol, 10.0 equiv) was placed in a 10 mL rb flask and heated to 170 ºC under 1 mm Hg vacuum. After 16 h at 170 ºC, the dried $CeCl_3$ was cooled to rt, and the flask was purged with N_2. THF (2.5 mL) was added via syringe, and the mixture was stirred at rt for 2 h.

Meanwhile, a 25 mL three-necked rb flask equipped with a condenser and a magnetic stir bar was charged with magnesium turnings (124.0 mg, 5 mmol, 1.0 equiv), and a crystal of iodine. The flask was heated with a heat gun for 5 min while stirring. THF (5.0 mL) was added via syringe, and the reaction mixture was heated with a heat gun to reflux. Chloromethyl trimethylsilane (0.613 g, 5.0 mmol, 1.0 equiv) was then added dropwise via syringe. The mixture was then stirred at rt for 1.5 h to give an assumed 1.0 M solution of $TMSCH_2MgCl$.

The $CeCl_3$/THF mixture was cooled to -78 ºC, then a solution of $TMSCH_2MgCl$ (2.03 mL of 1.0 M, 2.03 mmol, 10.0 equiv) was added dropwise via syringe. After 1 h at -78 ºC, a solution of ester **2.56** (167.2 mg, 0.203 mmol, 1.0 equiv) in THF (1.0 mL) was then added via cannula. An additional THF (0.6 mL) rinse was used to transfer the remaining ester residue into the reaction mixture. The solution was allowed to warm to rt and stirred overnight. The mixture was then recooled to -78 ºC, and then a 1N HCl solution (4.0 mL) was added dropwise via syringe. The reaction mixture was then warmed to rt and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 10 mL). The organic phases were combined, washed with saturated aqueous $NaHCO_3$ solution (10 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 12 cm silica gel column, eluting with 50% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (19-22) were combined and concentrated under reduced pressure to give the product **2.57** (103.4 mg, 71%) as a colorless oil: R_f = 0.31 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = +15.8 (c = 1.04, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.69 (dd, J = 11.4, 1.7 Hz, 2H), 7.68 (dd, J = 4.4, 1.3 Hz, 2H), 7.46-7.38 (m, 6H), 7.21 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.67 (dd, J = 14.1, 2.0 Hz, 2H), 4.46 (d, J = 11.1 Hz, 1H), 4.37 (d, J = 11.1 Hz, 1H), 4.00-3.94 (m, 1H), 3.81-3.74 (m, 6H), 3.60-3.50 (m, 2H), 3.44 (bs, 1H), 2.22 (dd, J = 13.8, 7.1 Hz, 1H), 2.07 (dd, J = 13.8, 6.0 Hz, 1H), 1.96 (ddd, J = 12.1, 2.4, 2.0 Hz, 1H), 1.87 (ddd, J = 12.4, 2.4, 2.4 Hz, 1H), 1.84-1.78 (m, 3H), 1.72-1.60 (m, 5H), 1.57 (s, 2H), 1.07 (s, 9H), 0.05 (s, 9H); 125 MHZ ^{13}C NMR ($CDCl_3$) δ 159.3, 144.6, 135.8, 134.0, 134.0, 131.1, 129.8, 129.7, 127.8, 127.8 114.0, 110.1, 76.3, 72.8, 72.5, 71.6, 69.5, 67.8, 60.5, 55.4, 46.6, 42.4,

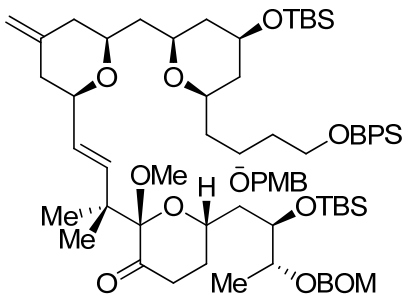
41.8, 41.6, 41.5, 37.5, 27.1, 27.1, 19.3, -1.2; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.4, 27.1, -1.2; CH_2 δ 101.1, 71.6, 60.5, 46.6, 42.4, 41.8, 41.6, 41.5, 37.5, 27.1; CH δ 135.8, 129.8, 129.7, 127.8, 127.8, 114.0, 76.3, 72.8, 72.5, 69.5, 67.8 CH0 δ 159.3, 144.6, 134.0, 134.0, 131.1, 19.3; IR (neat) 3441, 2941, 1612, 1513, 1427, 1248, 1111, 1037, 848, 738, 702, 614, 541, 505 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{42}H_{62}O_6NaSi_2$ (M+Na) 741.3977, found 741.3979.



Preparation of (2*S*,6*S*)-6-((2*R*,3*R*)-3-(benzyloxy methoxy)-2-(*tert*-butyldimeth yl silyloxy)butyl)-2-((*E*)-4-(6-(((4*S*)-6-((*S*)-4-(*tert*-butyl diphenylsilyloxy)-2-(4-methox y benzy loxy) butyl)-4-hydroxytetrahydro-2H-pyran-2-yl)methyl)-4-methylene tetra hydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxydihydro-2H-pyran-3(4H)-one (2.66). To a solution of hydroxyallylsilane **2.56** (31.6 mg, 0.0439 mmol, 1.1 equiv) and aldehyde **2.37** (21.9 mg, 0.0399 mmol, 1.0 equiv) in Et_2O (4.0 mL, 0.01M) in a 10 mL rb flask at -78 ºC was added a solution of TMSOTf in Et_2O (47.9 μL of 1.0 M, 0.0479 mmol, 1.2 equiv) dropwise via syringe. After 1 h at -78 ºC, the reaction mixture was quenched by the addition of diisopropylethylamine (0.2 mL), followed by the addition of saturated aqueous $NaHCO_3$ solution (2 mL). The mixture was warmed to rt, then the phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated

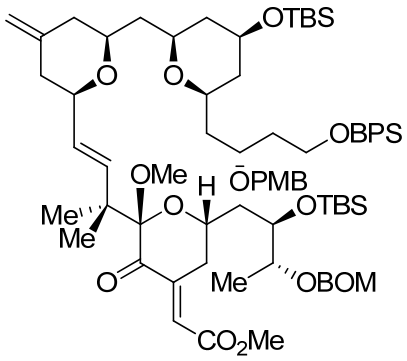
under reduced pressure. Purification was accomplished by flash chromatography column on a 3 × 12 cm silica gel column, eluting with 40% EtOAc/hexanes, collecting 13 × 100 mm test tube fractions. The product containing fractions (7-15) were combined and concentrated under reduced pressure to give the product **2.66** (43.0 mg, 92%) as a colorless oil: R_f = 0.38 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = +14 (*c* = 0.08, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-7.66 (m, 4H), 7.45-7.34 (m, 11H), 7.18 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.06 (dd, *J* = 16.1, 1.0 Hz, 1H), 5.45 (dd, *J* = 16.1, 6.0 Hz, 1H), 4.79 (d, *J* = 1.3 Hz, 2H), 4.66-4.58 (m, 2H), 4.63 (s, 2H), 4.46 (d, *J* = 11.1 Hz, 1H), 4.37 (d, *J* = 10.8 Hz, 1H), 4.13-4.04 (m, 2H), 3.95-3.89 (m, 1H), 3.84-3.76 (m, 9H), 3.60-3.46 (m, 3H), 3.29 (s, 3H), 2.45 (d, *J* = 6.4 Hz, 1H), 2.43 (d, *J* = 5.7 Hz, 1H), 2.24 (d, *J* = 13.1 Hz, 1H), 2.18 (d, *J* = 13.4 Hz, 1H), 2.02-1.91 (m, 6H), 1.91-1.84 (m, 2H), 1.83-1.71 (m, 2H), 1.68-1.48 (m, 6H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.05 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 207.7, 159.3, 144.3, 138.0, 137.2, 135.8 (×2), 134.1, 134.0, 131.2, 129.8, 129.6, 129.1, 128.6 (×2), 128.0 (×2), 127.9 (×2), 114.0, 109.1, 104.1, 93.4, 79.1, 75.2, 75.0, 72.7, 72.1, 72.0 (×2), 70.7, 69.9, 69.6, 68.4, 60.6, 55.5, 55.5, 52.8, 44.4, 42.5, 42.3, 41.8, 41.4, 41.2, 40.5, 38.2, 37.9, 37.7, 30.6, 27.1, 26.1, 23.2, 22.1, 19.4, 18.3, 13.9, -3.8, -4.5; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 52.8, 27.1, 26.1, 23.2, 22.1, 13.9, -3.9, -4.5; CH_2 δ 109.1, 93.4, 72.0, 69.6, 60.6, 42.5, 42.3, 41.8, 41.4, 41.2, 40.5, 38.2, 37.9, 37.7, 30.6; CH δ 137.2, 135.8 (×2), 129.8, 129.6, 129.1, 128.6 (×2), 128.0 (×2), 127.9 (×2), 114.0, 79.1, 75.2, 75.0, 72.7, 72.1, 72.0, 70.7, 69.9, 68.4, CH0 δ 207.7, 159.3, 144.3, 138.0, 134.1, 134.0, 131.2, 104.1, 44.4, 19.4, 18.3; IR (neat) 3445, 2931, 2857, 1724, 1612, 1513, 1465, 1383, 1251, 1110,

1042, 835, 776, 739, 702, 612, 536 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{69}H_{100}O_{12}NaSi_2$ (M+Na) 1199.6646, found 1199.6636.



Preparation of (2*S*,6*S*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(*tert*-butyldi met hylsilyloxy) butyl)-2-((*E*)-4-((2R,6S)-6-(((2*S*,4*S*,6*R*)-4-(*tert*-butyldimethyl silyloxy)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)butyl)tetrahydro-2H-pyra n-2-yl)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-met hoxy dihydro-2H-pyran-3(4H)-one (1.145). To a solution of alcohol **1.144** (83.8 mg, 0.0712 mmol, 1.0 equiv) in CH_2Cl_2 (7.1 mL, 0.01M) in a 25 mL rb flask at 0 ºC were added diisopropylethylamine (45.8 mg, 0.427 mmol, 6.0 equiv) and TBSOTf (47.0 mg, 0.178 mmol, 2.5 equiv) via syringe. The solution was stirred at 0 ºC for 40 min, then quenched by the addition of 1.0 mL of methanol. Stirring was continued for another 10 min, and then saturated aqueous $NaHCO_3$ solution (5 mL) was added. The aqueous phase was separated and extracted with CH_2Cl_2 (3×10 mL). The organic phases were combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 4×10 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 18×150 mm test tube fractions. The product containing fractions (6-13) were combined and concentrated under reduced pressure to give the product **2.64** (89.3 mg, 98% yield) as a colorless oil: R_f = 0.73 (20%

EtOAc/hexanes); $[\alpha]_D^{20}$ = +8.1 (*c* = 0.40, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.70-7.66 (m, 4H), 7.44-7.35 (m, 11H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 6.02 (d, *J* = 5.6 Hz, 1H), 5.47 (dd, *J* = 16.1, 6.3 Hz, 1H), 4.78 (ABq, *J* = 7.3, Δν = 6.9 Hz, 2H), 4.65 (s, 1H), 4.63 (s, 2H), 4.56 (s, 1H), 4.46 (d, *J* = 10.7 Hz, 1H), 4.38 (d, *J* = 10.7 Hz, 1H), 4.14-4.04 (m, 2H), 3.95-3.88 (m, 1H), 3.85-3.71 (m, 8H), 3.60-3.50 (m, 2H), 3.50-3.44 (m, 1H), 3.29 (s, 3H), 2.43 (dd, *J* = 8.3, 5.9 Hz, 2H), 2.29 (d, *J* = 13.2 Hz, 1H), 2.17 (d, *J* = 13.2 Hz, 1H), 2.04-1.90 (m, 6H), 1.86-1.72 (m, 5H), 1.68-1.48 (m, 5H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.12 (s, 3H), 1.09 (s, 3H), 1.06 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 207.4, 159.3, 144.4, 138.1, 137.1, 135.8 (×2), 134.1, 134.0, 131.3, 129.8 (×2), 129.6, 129.4, 128.6, 128.0, 127.9 (×2), 114.0, 109.0, 104.1, 93.4, 79.2, 75.3, 75.1, 72.9, 72.2, 72.0, 72.0, 70.8, 69.9, 69.6, 69.1, 60.6, 55.5, 52.8, 44.4, 42.8, 42.5, 42.5, 42.1, 41.2, 40.4, 38.2, 38.0, 37.7, 30.7, 27.2, 26.1 (×2), 23.3, 21.9, 19.4, 18.3, 18.3, 14.0, -3.9, -4.2, -4.3, -4.4; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 52.8, 27.2, 26.1 (×2), 23.3, 21.9, 14.0, -3.9, -4.2, -4.3, -4.4; CH_2 δ 109.0, 93.4, 72.2, 69.6, 60.6, 42.8, 42.5, 42.5, 42.1, 41.2, 40.4, 38.2, 38.0, 37.7, 30.7; CH δ 137.1, 135.8 (×2), 129.8 (×2), 129.6, 129.4, 128.6, 128.0, 127.9 (×2), 114.0, 79.2, 75.3, 75.1, 72.9, 72.0, 72.0, 70.8, 69.9, 69.1, CH0 δ 207.4, 159.3, 144.4, 138.1, 134.1, 134.0, 131.3, 104.1, 44.4, 19.4, 18.3, 18.3; IR (neat) 2930, 2856, 1728, 1513, 1465, 1382, 1250, 1110, 835, 775, 738, 703, 536cm^{-1}; HRMS (ESI/TOF) calcd for $C_{75}H_{114}O_{12}NaSi_3$ (M+Na) 1313.7516, found 1313.7560.

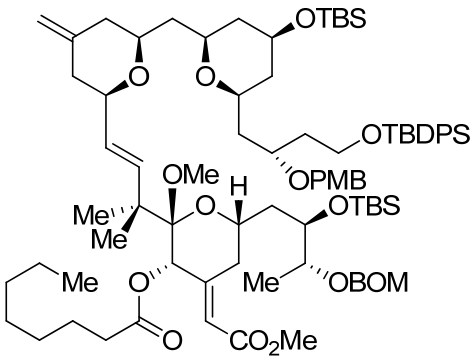


Preparation of (*E*)-methyl 2-((2*S*,6*S*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(*tert*-butyl dimethylsilyloxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*S*,4*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)butyl)tetrahydro-2H-pyran-2-yl)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-3-oxo-2H-pyran-4(3H,5H,6H)-ylidene) acetate (2.67). To a stirring solution of ketone **2.65** (63.2 mg, 0.0489 mmol, 1.0 equiv) in THF (0.98 mL, 0.05M) in a 10 mL rb flask at -78 °C was added a freshly prepared solution of LDA in THF (0.587 mL of 0.25 M, 0.147 mmol, 3.0 equiv). The mixture was stirred at -78 °C for 30 min, then a solution of methyl glyoxylate in THF (0.489 mL of 3.0 M, 1.47 mmol, 30 equiv) was added via syringe. The reaction mixture stirred at -78 ºC for 30 min and was then quenched by the addition of saturated aqueous NH_4Cl solution (1.0 mL). The mixture was warmed to rt and was then partitioned between 5 mL of EtOAc and 5 mL of brine. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 4 × 11 cm silica gel column, eluting with 15% EtOAc/hexanes, collecting 18 × 150 mm test tube fractions. The product containing fractions (9-23) were

combined and concentrated under reduced pressure to give a diastereomeric mixture of products (62.1 mg, 92% yield), which were carried into the next step.

To a stirring solution of the aforementioned product (62.1mg, 0.0450 mmol, 1.0 equiv) in pyridine (4.5 mL, 0.01 M) in a 25 mL rb flask with a condenser were added 4-dimethylaminopyridine (5.5 mg, 0.040 mmol, 1.0 equiv) and a solution of Ac_2O in CH_2Cl_2 (1.80 mL of 0.5 M, 0.890 mmol, 20 equiv) via syringe. The reaction mixture was heated to 60 °C and stirred overnight. The solution was cooled to rt, and then was then partitioned between 10 mL of CH_2Cl_2 and 5 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 12 cm silica gel column, eluting with 10% EtOAc/hexanes, collecting 18 × 150 mm test tube fractions. The product containing fractions (4-9) were combined and concentrated under reduced pressure to give the product **2.67** (57.2 mg, 93% yield) as a yellow oil: R_f = 0.71 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = -16.1 (*c* = 0.90, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.67 (m, 4H), 7.45-7.28 (m, 11H), 7.19 (d, *J* = 8.1Hz, 2H), 6.86 (d, *J* = 7.7 Hz, 2H), 6.55 (t, *J* = 1.7 Hz, 1H), 5.82 (d, *J* = 15.8 Hz, 1H), 5.38 (dd, *J* = 16.1, 6.4Hz, 1H), 4.79 (ABq, *J* = 7.1 Hz, Δν = 8.5 Hz, 2H), 4.65-4.60 (m, 3H), 4.55 (s, 1H), 4.47 (d, *J* = 10.4 Hz, 1H), 4.37 (d, *J* = 10.4 Hz, 1H), 4.11-.4.05 (m, 2H), 3.95-3.89 (m, 1H), 3.86-3.77 (m, 6H), 3.77-3.71 (m, 4H), 3.71-3.65 (m, 1H), 3.59-3.50 (m, 2H), 3.50-3.43 (m, 1H), 3.32 (s, 3H), 2.86 (ddd, *J* = 15.8, 12.4, 3.0 Hz, 1H), 2.28 (d, *J* = 12.8 Hz, 1H), 2.09 (ddd, *J* = 10.1, 7.7, 2.4Hz, 1H), 2.04 (d, *J* = 13.8 Hz, 1H), 1.98 (ddd, *J* = 13.8, 8.1, 5.7 Hz, 1H), 1.90 (t, *J* = 11.1 Hz, 2H), 1.85-1.72 (m, 4H), 1.69-1.60 (m, 2H), 1.60-1.50 (m, 2H), 1.29-1.20 (m,

3H), 1.17 (d, J = 6.0 Hz, 3H), 1.11 (s, 3H), 1.07 (s, 9H), 1.04 (s, 3H), 0.90 (s, 9H), 0.86 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.03 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 197.5, 166.3, 159.3, 148.3, 144.2, 138.0, 136.1, 135.8, 134.1, 134.0, 131.2, 130.1, 129.8, 129.6, 128.6, 128.0 (×2), 127.9, 123.2, 114.0, 109.0, 104.6, 93.5, 79.2, 75.3, 75.1, 72.9, 72.3, 72.0, 71.9, 71.0, 69.9, 69.6, 69.0, 60.5, 55.5, 52.4, 52.0, 44.8, 42.7, 42.5, 42.4, 42.0, 40.6, 40.3, 38.4, 37.9, 36.6, 27.2, 26.1, 26.0, 22.8, 21.4, 19.4, 18.3, 18.2, 13.9, -3.8, -4.3, -4.3, -4.5; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 52.4, 52.0, 27.2, 26.1, 26.0, 22.8, 21.4, 13.9, -3.8, -4.3, -4.3, -4.5 ; CH_2 δ 109.0, 93.5, 72.3, 69.6, 60.5, 42.7, 42.5, 42.4, 42.0, 40.6, 40.3, 38.4, 37.9, 36.6; CH δ 136.1, 135.8, 130.1, 129.8, 129.6, 128.6, 128.0 (×2), 127.9, 123.2, 114.0, 79.2, 75.3, 75.1, 72.9, 72.0, 71.9, 71.0, 69.9, 69.0; CH_0 δ 197.5, 166.3, 159.3, 148.3, 144.2, 138.0, 134.1, 134.0, 131.2, 104.6, 44.8, 19.4, 18.3, 18.2; IR (neat) 2934, 2857, 1724, 1513, 1466, 1381, 1250, 1111, 835, 775, 738, 703, 536 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{78}H_{116}O_{14}NaSi_3$ (M+Na) 1383.7565, found 1383.7555.

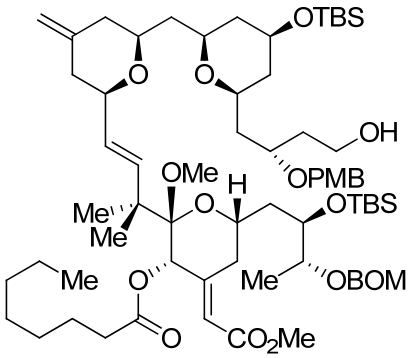


Preparation of (2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(*tert*-butyldimethylsilyloxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*S*,4*S*,6*R*)-4-(*tert*-butyldimethylsilyloxy)-6-((*S*)-4-(*tert*-butyldiphenylsilyloxy)-2-(4-methoxybenzyloxy)butyl) tetrahydro-2H-pyran-2-yl)methyl)-4-methylene tetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-

2-ethoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2H-pyran-3-yl octanoate (2.64). To a stirring solution of ketone **2.67** (14.1 mg, 0.0104 mmol, 1.0 equiv) in methanol (2.1 mL, 0.005M) in a 10 mL rb flask at rt was added $CeCl_3 \cdot 7H_2O$ (77.5 mg, 0.208 mmol, 20 equiv). The reaction mixture was stirred at rt until all the $CeCl_3 \cdot 7H_2O$ crystals had dissolved. The reaction mixture was then cooled to -40 °C and kept for 15 min. $NaBH_4$ (3.9 mg, 0.104 mmol, 10 equiv) was then added in one portion. The mixture was stirred at -40 °C for 3 h, then diluted with 40% EtOAC/hexanes (10 mL), and quenched by the addition of saturated aqueous NH_4Cl solution (5 mL). The mixture was poured into a separatory funnel with the aid of 50 mL of 40% EtOAc/hexanes. The organic phase was separated, then washed with 10 mL of H_2O and 10 mL of brine, then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was used in the next step without further purification.

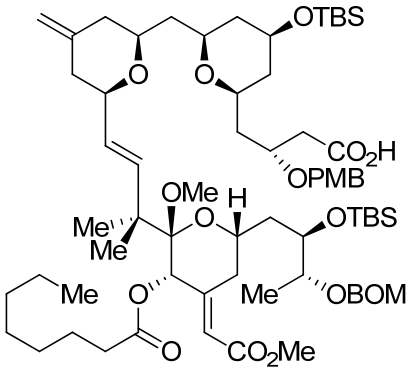
To a stirring solution of the aforementioned crude alcohol in CH_2Cl_2 (1.1 mL, 0.01M) in a 10 mL rb flask at rt, were added pyridine (8.2 mg, 0.104 mmol, 10 equiv), 4-dimethylaminopyridine (2.5 mg, 0.0208 mmol, 2.0 equiv), and octanoic anhydride (14.1 mg, 0.052 mmol, 5.0 equiv). The reaction mixture stirred at rt overnight, then diluted with 10 mL of CH_2Cl_2. The mixture was poured into a separatory funnel containing 5 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with CH_2Cl_2 (3×15 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2×16 cm silica gel column, eluting with 8% EtOAc/hexanes, collecting 13×100 mm test tube fractions. The product containing fractions (9-15) were combined and concentrated under reduced pressure to give the product **2.64** (12.6 mg, 82%

yield) as a colorless oil. R_f = 0.60 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +3.2 (*c* = 1.45, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.69-7.65 (m, 4H), 7.44-7.34 (m, 11H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.93 (d, *J* = 16.1 Hz), 5.88 (s, 1H), 5.57 (s, 1H), 5.43 (dd, *J* = 16.1, 5.9 Hz, 1H), 4.80 (s, 2H), 4.64 (s, 3H), 4.55 (s, 1H), 4.44 (d, *J* = 10.8 Hz, 1H), 4.36 (d, *J* = 10.3 Hz, 1H), 4.12-4.06 (m, 2H), 3.92-3.86 (m, 1H), 3.84 (dd, *J* = 6.4, 4.4 Hz, 1H), 3.81 (s, 3H), 3.80-3.70 (m, 4H), 3.79 (s, 3H), 3.57-3.44 (m, 4H), 3.30 (s, 3H), 2.35 (ddd, *J* = 7.3, 7.3, 1.5 Hz, 2H), 2.29 (d, *J* = 13.2 Hz, 1H), 2.17 (d, *J* = 12.7 Hz, 1H), 2.03-1.95 (m, 3H), 1.90 (t, *J* = 12.2 Hz, 1H), 1.85-1.72 (m, 4H), 1.65-1.52 (m, 6H), 1.33-1.28 (m, 10H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.11 (s, 3H), 1.11 (s, 3H), 1.04 (s, 9H), 0.92-0.85 (m, 21H), 0.08 (s, 3H), 0.06 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.3, 166.6, 159.4, 153.1, 144.4, 138.2, 138.0, 135.8 (×2), 134.1 (×2), 131.3, 129.8 (×2), 129.5, 128.6, 128.0, 127.9, 127.8, 127.5, 117.0, 114.1, 109.0, 102.7, 93.3, 79.1, 75.2, 75.1, 73.0, 72.2 (×2), 72.0, 71.6, 70.4, 69.5, 69.1, 68.5, 60.6, 55.5, 51.6, 51.3, 46.1, 42.8, 42.5, 42.5, 42.1, 40.8, 40.4, 38.8, 38.0, 34.6, 33.6, 31.9, 29.3, 29.2, 27.2, 26.1, 25.0, 24.2, 24.2, 22.8, 19.4, 18.3 (×2), 14.3, 14.0, -3.8, -4.2, -4.3, -4.4; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 51.6, 51.3, 27.2, 26.1, 26.1, 24.2, 24.2, 14.3, 14.0, -3.8, -4.2, -4.3, -4.4; CH_2 δ 109.0, 93.3, 72.2, 69.5, 60.6, 42.8, 42.5, 42.5, 42.1, 40.8, 40.4, 38.8, 38.0, 34.6, 33.6, 31.9, 29.3, 29.2, 25.0, 22.8; CH δ 138.0, 135.8 (×2), 129.8 (×2), 129.5, 128.6, 128.0, 127.9, 127.5, 117.0, 114.0, 79.1, 75.2, 75.1, 73.0, 72.0 (×2), 71.6, 70.4, 69.1, 68.5; CH0 δ 172.3, 166.6, 159.4, 153.1, 144.4, 138.2, 134.1 (×2), 131.3, 127.8, 102.7, 46.1, 19.4, 18.3 (×2); IR (neat) 2931, 2857, 1722, 1513, 1465, 1381, 1251, 1154, 1111, 836, 775, 739, 702 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{86}H_{132}O_{15}NaSi_3$ (M+Na) 1511.8772, found 1511.8793.



Preparation of (2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(benzyloxy methoxy)-2-(*tert*-butyl dimethyl silyloxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*S*,4*S*,6*R*)-4-(*tert*-butyl dimethylsilyl oxy)-6-((*S*)-4-hydroxy-2-(4-methoxy benzyloxy)butyl)tetrahydro-2H-pyran-2-yl)met hyl)-4-methylene tetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethy lidene) tetrahydro-2H-pyran-3-yl octanoate (2.68). To a stirring solution of silyl ether **2.64** (11.0 mg, 0.00738 mmol, 1.0 equiv) in DMF (0.738 mL, 0.01 M) in a 4 mL reaction vial, were added a solution of TBAF solution in THF (7.4 μL of 1.0 M, 0.00738 mmol, 1.0 equiv) and a solution of acetic acid solution in DMF (7.4 μL of 1.0 M, 0.00738 mmol, 1.0 equiv). The solution was stirred at rt for 1 d, then diluted with 40% EtOAc/hexanes (5 mL) and quenched with water (5 mL). The phases were separated and the aqueous phase was extracted with 40% EtOAc/hexanes (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash chromatography on a 2 × 13 cm silica gel column, eluting with 20% EtOAc/hexanes, collecting 13 × 100 mm test tube fractions. The product containing fractions (10-20) were combined and concentrated under reduced pressure to provide the product alcohol **2.68** (8.2 mg, 89%) as a colorless oil. R_f = 0.44 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +7.4 (*c* = 0.575, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.36-7.34 (m, 5H), 7.27 (d, *J* = 8.3 Hz), 6.89 (d, *J* = 8.3 Hz,

2H), 5.94 (d, *J* = 16.1 Hz, 1H), 5.89 (s, 1H), 5.57 (s, 1H), 5.42 (dd, *J* = 16.1, 5.9 Hz, 1H), 4.80 (s, 2H), 4.66 (s, 1H), 4.65 (s, 2H), 4.57 (s, 1H), 4.50 (d, *J* = 10.7 Hz, 1H), 4.45 (d, *J* = 10.7 Hz, 1H), 4.12-4.06 (m, 2H), 3.92-3.82 (m, 2H), 3.82-3.75 (m, 5H), 3.75-3.65 (m, 5H), 3.55-3.40 (m, 4H), 3.30 (s, 3H), 2.39-2.32 (m, 3H), 2.28 (d, *J* = 13.2 Hz, 1H), 2.18 (d, *J* = 13.2 Hz, 1H), 2.00 (q, *J* = 12.2 Hz, 2H), 1.95-1.86 (m, 3H), 1.84-1.66 (m, 4H), 1.66-1.50 (m, 6H), 1.38-1.20 (m, 10H), 1.16 (d, *J* = 6.3 Hz, 3H), 1.12 (s, 6H), 0.90-0.84 (m, 21H), 0.08 (s, 3H), 0.06 (s, 3H). 0.06 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.4, 166.7, 159.6, 153.1, 144.5, 138.4, 138.1, 130.7, 129.7, 128.6, 128.0, 127.9, 127.3, 117.0, 114.2, 109.0, 102.6, 93.3, 79.4, 75.5, 75.2, 75.1, 72.5, 72.2 (×2), 71.6, 70.3, 69.5, 68.9, 68.4, 60.4, 55.5, 51.6, 51.3, 46.1, 42.8, 42.5, 42.0, 41.7, 40.9, 40.4, 38.7, 36.9, 36.8, 34.6, 31.9, 29.3, 29.2, 26.1, 26.1, 25.0, 24.2, 24.1, 22.8, 18.3, 18.3, 14.3, 14.0, -3.8, -4.3, -4.4; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 51.6, 51.3, 26.1, 26.1, 24.2, 24.1, 14.3, 14.0, -3.8, -4.3, -4.4 ; CH_2 δ 109.0, 93.3, 72.2, 69.5, 60.4, 42.8, 42.5, 42.0, 41.7, 40.9, 40.4, 38.7, 36.9, 36.8, 34.6, 31.9, 29.3, 29.2, 25.0, 22.8; CH δ 138.4, 129.7, 128.6, 128.0, 127.9, 127.3, 117.0, 114.2, 79.4, 75.5, 75.2, 75.1, 72.5, 72.2, 71.6, 70.3, 68.9, 68.4; CH_0 δ 172.4, 166.7, 159.6, 153.1, 144.5, 138.1, 130.7, 102.6, 46.1, 18.3, 18.3; IR (neat) 2930, 2857, 1722, 1514, 1463, 1380, 1250, 1155, 1044, 836, 775 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{70}H_{114}O_{15}NaSi_2$ (M+Na) 1273.7594, found 1273.7595.

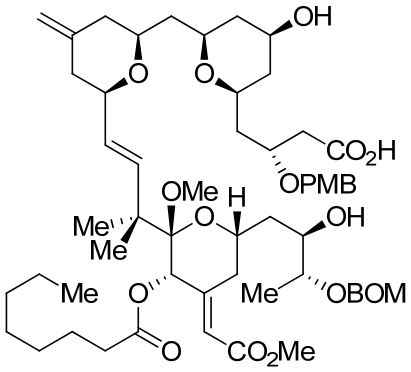


Preparation of (*R*)-4-((2*R*,4*S*,6*S*)-6-(((2*S*,6*R*)-6-((*E*)-3-((2*S*,3*S*,6*S*,*E*)-6-((2*R*, 3*R*)-3-(benzyloxy methoxy)-2-(*tert*-butyldimethylsilyloxy) butyl)-2-methoxy-4-(2-me thoxy-2-oxoethylidene)-3-(octanoyloxy)tetrahydro-2H-pyran-2-yl)-3-methylbut-1-en yl)-4-methylene tetrahydro-2H-pyran-2-yl)methyl)-4-(tert-butyldimethyl silyloxy) te trahydro-2H-pyran-2-yl)-3-(4-methoxy benzyloxy) butanoic acid (2.69). To a stirring solution of alcohol **2.68** (7.1 mg, 0.0057 mmol, 1.0 equiv) in CH_2Cl_2 (0.57 mL), in a 4 mL reaction vial at 0 °C, were added diisopropylethylamine (21 μL, 0.119 mmol, 21.0 equiv) and DMSO (12 μL, 0.171 mmol, 30.0 equiv). The solution was stirred at 0 °C for 5 min and $SO_3 \cdot py$ (5.4 mg, 0.0340 mmol, 6.0 equiv) was added in one portion. Stirring continued at 0 °C for 1.25 h, after which the reaction mixture was diluted with CH_2Cl_2 (1 mL) and quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL). The mixture was stirred at rt for 10 min until effervescence was complete. The reaction mixture was then partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was washed through a small plug of silica gel with 20 % EtOAc/hexanes (30 mL), and the solvent was removed under reduced pressure to provide the aldehyde, which was used in the next step without further purification.

To a stirring solution of the aforementioned aldehyde (7.1 mg, 0.0057 mmol, 1.0 equiv) in 2-methyl-2-butene (570 μL) and *tert*-butyl alcohol (570 μL), in a 4 mL reaction vial at rt, was added a aqueous KH_2PO_4 solution (109 μL of 1.25 M). The mixture was cooled to -10 °C, and $NaClO_2$ (80% Aldrich, 13 mg, 0.114 mmol, 20.0 equiv) was added

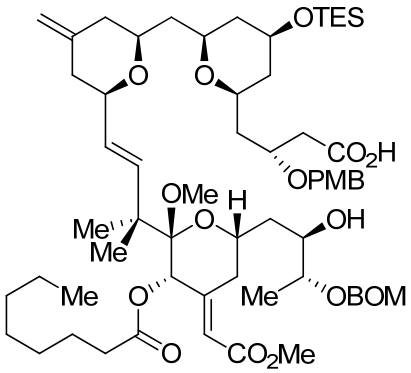
in one portion. The reaction mixture stirred vigorously at -10 °C for 4 h, and was then quenched with the addition of aqueous pH 4 buffer solution (1 mL). The reaction mixture was partitioned between CH_2Cl_2 (5 mL) and aqueous pH 4 buffer solution (5 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification was accomplished using flash chromatography on a 0.8 × 6.5 cm silica gel column, eluting with 20 % EtOAc/hexanes then 1 % methanol / 30 % EtOAc/hexanes, collecting 6 × 50 mm test tube fractions. The product containing fractions (10-21) were combined and concentrated under reduced pressure to provide pure carboxylic acid **2.69** (8.0 mg, quant. yield over 2 steps) as a colorless oil: R_f = 0.38 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = +12 (*c* = 0.27, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.28 (m, 5H), 7.36 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.96 (d, *J* = 5.8 Hz, 1H), 5.88 (s, 1H), 5.59 (s, 1H), 5.44 (dd, *J* = 15.8, 6.1 Hz, 1H), 4.82 (ABq, *J* = 7.1 Hz, Δν = 7.2 Hz, 2H), 4.66 (s, 2H), 4.60 (s, 1H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.14-4.05 (m, 3H), 3.87 (ddd, *J* = 12.4, 6.4, 6.4 Hz, 1H), 3.81 (s, 3H), 3.77 (t, *J* = 5.0 Hz, 1H), 3.75-3.68 (m, 4H), 3.57-3.40 (m, 4H), 3.31 (s, 3H), 2.61 (dddd, *J* = 15.4, 15.4, 15.4, 5.4 Hz, 2H), 2.40-2.31 (m, 3H), 2.28 (d, *J* = 13.1 Hz, 1H), 2.17 (d, *J* = 12.4 Hz, 1H), 2.08-1.88 (m, 5H), 1.84-1.72 (m, 3H), 1.70-1.52 (m, 5H), 1.35-1.25 (m, 10H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.12 (s, 6H), 0.90-0.86 (m, 21H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 173.2, 172.5, 166.8, 159.6, 153.2, 144.3, 138.8, 137.9, 130.3, 129.7, 128.6, 128.1, 127.9, 127.2, 116.9, 114.2, 109.1, 102.6, 93.1, 79.6, 75.3, 75.1, 73.3, 72.5, 72.2, 72.1, 71.6, 70.1, 69.5, 68.8, 68.4, 55.5, 51.6, 51.4, 46.1, 42.8, 42.2, 42.0, 42.0, 40.8, 40.4, 40.0, 38.7, 34.6, 33.6, 31.9, 29.3, 29.2, 26.1

(×2), 25.0, 24.4, 24.0, 22.8, 18.3 (×2), 14.3, 14.0, -3.8, -4.3, -4.5; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 51.6, 51.4, 26.1 (×2), 24.4, 24.0, 14.3, 14.0, -3.8, -4.3, -4.5 ; CH_2 δ 109.1, 93.1, 72.5, 69.5, 42.8, 42.2, 42.0, 42.0, 40.8, 40.4, 40.0, 38.7, 34.6, 33.6, 31.9, 29.3, 29.2, 25.0, 22.8; CH δ 138.8, 129.7, 128.6, 128.1, 127.9, 127.2, 116.9, 114.1, 79.6, 75.3, 75.1, 73.3, 72.2, 72.1, 71.6, 70.1, 68.8, 68.4; CH0 δ 173.2, 172.5, 166.8, 159.6, 153.2, 144.3, 137.9, 130.3, 102.6, 46.1, 18.3 (×2); IR (neat) 2930, 2857, 1722, 1514, 1463, 1380, 1250, 1156, 1111, 836, 775, 542 cm^{-1} ; HRMS (ESI/TOF) calcd for $C_{70}H_{112}O_{16}NaSi_2$ (M+Na) 1287.7381, found 1287.7361.



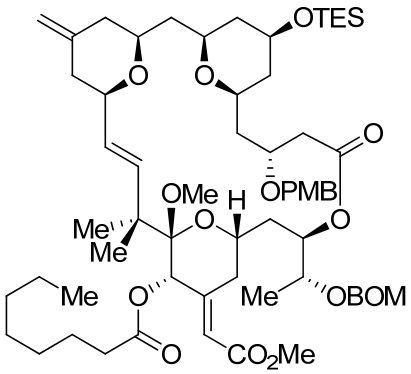
Preparation of (*R*)-4-((2*S*,4*S*,6*R*)-6-(((2*S*,6*R*)-6-((*E*)-3-((2*S*,3*S*,6*S*,*E*)-6-((2*R*, 3*R*)-3-(benzyloxy methoxy)-2-hydroxybutyl)-2-methoxy-4-(2-methoxy-2-oxoethyli de ne)-3-(octanoyloxy) tetra hydro-2H-pyran-2-yl)-3-methylbut-1-enyl)-4-methylenete trahydro-2H-pyran-2-yl) methyl)-4-hydroxy tetrahydro-2H-pyran-2-yl)-3-(4-meth oxy benzyloxy) butanoic acid (2.70). To a stirring solution of TBS ether **2.69** (7.6 mg, 0.0060 mmol, 1.0 equiv) in 9:1 THF/ pyridine (600 μL, 0.01 M) in a 4 mL plastic vial was added HF·Py (20 %, 240 μL). The solution was stirred at rt for 48 h, then diluted with 50 % EtOAc/hexanes (50 mL), and washed with brine (2 × 10 mL). The solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification

was accomplished using flash chromatography with a 2×14 cm silica gel column, eluting with 10% methanol/40% EtOAc/hexanes, collecting 10×130 mm test tube fractions. The product containing fractions (6-8) were combined and concentrated under reduced pressure to provide the product **2.70** (5.4 mg, 87%) as a colorless oil: R_f = 0.48 (10% methanol/40 %EtOAc/hexanes); $[\alpha]_D^{20}$ = +6 (*c* = 0.20, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.37-7.29 (m, 5H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.00 (d, *J* = 16.1 Hz, 1H), 5.87 (s, 1H), 5.54 (s, 1H), 5.40 (dd, *J* = 16.1, 6.4 Hz, 1H), 4.86 (ABq, *J* = 6.8 Hz, Δν = 20.5 Hz 2H), 4.70 (s, 2H), 4.66 (d, *J* = 2.9 Hz, 2H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.46 (d, *J* = 10.7 Hz, 1H), 4.22-4.16 (m, 1H), 4.14-4.06 (m, 2H), 3.89-3.84 (m, 1H), 3.80 (s, 3H), 3.78-3.72 (m, 2H), 3.70-3.62 (m, 5H), 3.52-3.40 (m, 4H), 3.33 (s, 3H), 2.65 (dd, *J* = 15.6, 5.9 Hz, 1H), 2.57 (dd, *J* = 15.6, 5.9 Hz, 1H), 2.40-2.32 (m, 3H), 2.26-2.18 (m, 3H), 2.05-1.85 (m, 5H), 1.80-1.55 (m, 7H), 1.34-1.24 (m, 10H), 1.18-1.08 (m, 9H), 0.88 (t, *J* = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 173.5, 172.3, 166.9, 159.6, 153.2, 144.4, 139.7, 137.7, 130.2, 129.7, 128.7, 128.1 (×2), 127.0, 116.8, 114.2, 109.1, 102.9, 93.9, 80.0, 77.9, 75.1, 72.9, 72.5, 72.2 (×2), 71.3, 70.1, 68.2, 68.2, 60.6, 55.5, 51.5, 51.4, 46.2, 42.2, 41.8, 41.5, 41.1, 40.8 (×2), 39.9, 34.7, 31.9, 29.9, 29.3, 29.1, 25.0, 24.9 (×2), 23.0, 22.8, 17.0, 14.3; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 51.5, 51.4, 25.0, 23.0, 17.0, 14.3; CH_2 δ 109.1, 93.9, 72.2, 70.1, 42.2, 41.8, 41.5, 41.1, 40.8 (×2), 39.9, 34.7, 31.9, 29.9, 29.3, 29.1, 24.9 (×2), 22.8; CH δ 139.7, 129.7, 128.7, 128.1 (×2), 127.0, 116.8, 114.2, 80.0, 77.9, 75.1, 72.9, 72.5, 72.2 (×2), 71.3, 68.2, 68.2; CH0 δ 173.5, 172.3, 166.9, 159.6, 153.3, 144.4, 137.7, 130.2, 102.9, 46.2; IR (neat) 3426, 2930, 1719, 1514, 1458, 1379, 1247, 1156, 1105, 1038, 745 cm^{-1}; HRMS (ESI/TOF) calcd $C_{58}H_{84}O_{16}Na$ for (M+Na) 1059.5657, found 1059.5675.



Preparation of (*R*)-4-((2*R*,4*S*,6*S*)-6-(((2*S*,6*R*)-6-((*E*)-3-((2*S*,3*S*,6*S*,*E*)-6-((2*R*, 3*R*)-3-(benzyloxy methoxy)-2-hydroxybutyl)-2-methoxy-4-(2-methoxy-2-oxoethylid ene)-3-(octanoyloxy) tetra hydro-2H-pyran-2-yl)-3-methylbut-1-enyl)-4-methylene tetrahydro-2H-pyran-2-yl)methyl)-4-(triethyl silyloxy)tetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyl oxy)butanoic acid (2.73). To a stirring solution of alcohol **2.70** (3.0 mg, 0.0029 mmol, 1.0 equiv) in CH_2Cl_2 (116 μL, 0.025 M) in a 4 mL reaction vial at rt was added 4-dimethylaminopyridine (1.6 mg, 0.013 mmol, 4.5 equiv). The solution was cooled to -15 °C, then a solution of TESCl in CH_2Cl_2 (6.1 μL of 1.0 M, 0.0061 mmol, 2.1 equiv) was added via syringe. The mixture was stirred at -15 °C for 90 min. The reaction mixture was then quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL), and the mixture was partitioned between 10 mL of EtOAc and 5 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with EtOAc (3×10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash chromatography on a 0.6×4 cm silica gel column, eluting with 5% methanol/35% EtOAc/hexanes, collecting 6×50 mm test tube fractions. The product containing fractions (11-25) were combined and concentrated under reduced pressure to provide

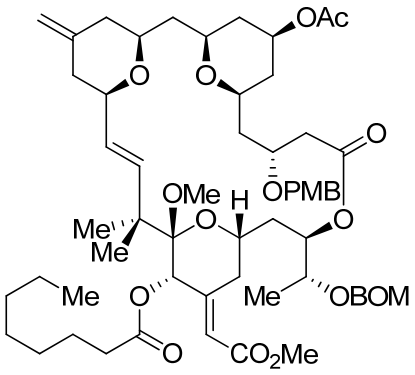
pure product **2.73** (2.5 mg, 76%) as a colorless oil: R_f = 0.63 (5% methanol/35% EtOAc/hexanes); $[\alpha]_D^{20}$ = +5 (*c* = 0.085, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.37-7.30 (m, 5H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.98 (d, *J* = 15.6 Hz, 1H), 5.88 (s, 1H), 5.56 (s, 1H), 5.42 (dd, *J* = 16.1, 6.3 Hz, 1H), 4.88 (ABq, J = 6.8 Hz, Δν = 19.5 Hz 2H), 4.70-4.60 (m, 4H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.47 (d, *J* = 10.7 Hz, 1H), 4.26-4.18 (m, 1H), 4.15-4.05 (m, 1H), 3.90-3.85 (m, 1H), 3.81 (s, 3H), 3.74-3.62 (m, 7H), 3.56-3.40 (m, 4H), 3.34 (s, 3H), 2.65 (dd, *J* = 15.6, 5.4 Hz, 1H), 2.57 (dd, *J* = 15.1, 5.4 Hz, 1H), 2.43-2.37 (m, 1H), 2.35 (ddd, *J* = 7.3, 7.3, 2.9 Hz, 2H), 2.28 (d, *J* = 13.2 Hz, 1H), 2.20 (d, *J* = 12.2 Hz, 1H), 2.10-2.00 (m, 2H), 2.00-1.88 (m, 3H), 1.86-1.80 (m, 1H), 1.80-1.55 (m, 7H), 1.34-1.22 (m, 10H), 1.12 (s, 6H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.88 (m, 6H), 0.60 (q, *J* = 7.8 Hz, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 174.0, 172.3, 166.8, 159.5, 153.2, 144.3, 139.2, 139.2, 137.7, 129.6, 128.7, 128.1, 128.1, 126.9, 116.8, 114.1, 109.1, 102.8, 93.9, 79.7, 78.0, 77.4, 75.7, 73.6, 72.4, 72.2, 72.1, 71.1, 70.1, 68.6, 68.2, 55.5, 51.4, 51.4, 46.2, 42.9, 42.3, 42.1, 40.8, 40.7, 39.8, 34.6, 31.9, 31.8, 29.9, 29.3, 29.2, 25.0, 24.6, 23.6, 22.9, 22.8, 17.0, 14.4, 7.1, 5.2; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 51.4, 51.4, 24.6, 23.6, 17.0, 14.4, 7.1; CH_2 δ 109.1, 93.9, 72.4, 70.1, 42.9, 42.3, 42.1, 40.8, 40.7, 39.8, 34.6, 31.9, 29.9, 29.3, 29.2, 25.0, 23.6, 22.9, 22.8, 5.2; CH δ 139.2, 139.2, 129.6, 128.7, 128.1, 128.1, 126.9, 114.1, 79.7, 78.0, 75.7, 73.6, 72.4, 72.2, 72.1, 71.1, 68.6, 68.2; CH0 δ 174.0, 172.3, 166.8, 159.5, 153.2, 144.3, 137.7, 116.8, 102.8, 46.2; IR (neat) 2930, 1719, 1513, 1459, 1380, 1247, 1154, 1040, 822, 742 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{64}H_{98}O_{16}NaSi$ (M+Na) 1173.6522, found 1173.6545.



Preparation of (1*S*,3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*,21*R*,23*R*,25*S*)-17-((*R*)-1-((benzyloxy)methoxy)ethyl)-11-methoxy-13-(2-methoxy-2-oxoethylidene)-21-((4-methoxybenzyl)oxy)-10,10-dimethyl-5-methylene-19-oxo-25-((triethylsilyl)oxy)-18,27,28,29-tetra oxatetra cyclo [21.3.1.13,7.111,15]nonacos-8-en-12-yl octanoate) (2.74). To a stirring solution of seco acid **2.73** (2.0 mg, 0.0017 mmol, 1.0 equiv) in THF (58 μL, 0.03 M) at 0 °C in a 4 mL reaction vial were added triethylamine (1.1 mg, 0.010 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (1.3 mg, 0.0052 mmol, 3.0 equiv) by syringe. The solution was stirred at 0 °C for 5 min, then warmed to rt and stirred for 2 h. The reaction mixture was diluted with 1:3 THF/toluene (696 μL, 0.0025 M), and taken up into a 1.0 mL gas-tight syringe. The resulting solution was added into a stirring solution of 4-dimethylaminopyridine (4.3 mg, 0.035 mmol, 20 equiv) in toluene (1.2 mL, 0.0015 M) in a 15 mL rb flask at 40 °C over 12 h by means of a syringe pump. The vial was rinsed with toluene (0.2 mL) and the rinsing solution was added into the reaction mixture by syringe pump over 2 h. The solution was cooled to rt and diluted with 50 mL of 40% EtOAc/hexanes. The solution was washed with saturated aqueous $NaHCO_3$ solution (5 mL) and brine (5 mL). The organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash chromatography on a 1.6 × 10 cm silica gel column, eluting with 20% EtOAc/hexanes,

collecting 12 × 75 mm test tube fractions. The product containing fractions (7-10) were combined and concentrated under reduced pressure to give the product macrolactone **2.74** (1.8 mg, 91%) as a colorless oil: R_f = 0.45 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +21 (*c* = 0.075, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) 7.40-7.28 (m, 5H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.22 (d, *J* = 6.1 Hz, 1H), 5.95 (s, 1H), 5.57 (ddd, *J* = 12.2, 4.0, 2.4 Hz, 1H), 5.34 (dd, *J* = 15.6, 8.3 Hz, 1H), 5.15 (s, 1H), 4.82 (ABq, *J* = 5.8 Hz, Δν = 10.1 Hz 2H), 4.75 (d, *J* = 3.9 Hz, 2H), 4.64 (ABq, *J* = 11.7 Hz, Δν = 16.8 Hz, 2H), 4.51 (s, 2H), 4.17 (m, 1H), 3.95 (m, 2H), 3.75 (s, 3H), 3.73-3.66 (m, 5H), 3.50 (m, 1H), 3.35 (t, *J* = 11.7 Hz, 1H), 3.15-3.05 (m, 4H), 3.08 (s, 3H), 2.54 (d, *J* = 15.6 Hz, 1H), 2.46 (dd, *J* = 15.6, 9.8 Hz, 1H), 2.32-2.26 (m, 3H), 2.20 (d, *J* = 12.7 Hz, 1H), 2.15-2.03 (m, 4H), 1.99 (d, *J* = 12.2 Hz, 1H), 1.94 (d, *J* = 12.7 Hz, 1H), 1.85 (t, *J* = 13.2 Hz, 1H), 1.83-1.67 (m, 3H), 1.64-1.55 (m, 2H), 1.52 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.46-1.38 (m, 1H), 1.30-1.22 (m, 10H), 1.09 (s, 3H), 1.08 (s, 3H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.95 (t, *J* = 7.8 Hz, 9H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.58 (q, *J* = 7.8 Hz, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.3, 172.2, 167.0, 159.3, 151.5, 144.7, 141.8, 138.1, 131.1, 129.6, 128.6, 128.1, 127.8, 125.7, 119.4, 113.9, 108.9, 103.4, 93.7, 81.5, 76.5, 75.3, 73.8, 73.7, 73.4, 73.2, 72.2, 70.7, 69.8, 68.6, 67.3, 55.5, 52.8, 51.4, 45.3, 44.2, 43.0, 42.2, 42.1 (×2), 41.5, 41.0, 34.8, 31.9, 31.1, 30.0, 29.2, 29.1, 26.4, 24.9, 22.8, 20.2, 15.3, 14.3, 7.1, 5.1; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 52.8, 51.4, 26.4, 20.2, 15.3, 14.3, 7.1; CH_2 δ 108.9, 93.7, 72.2, 69.8, 44.2, 43.0, 42.2, 42.1 (×2), 41.5, 41.0, 34.8, 31.9, 31.1, 30.0, 29.2, 29.1, 24.9, 22.8, 5.1; CH δ 141.8, 129.6, 128.6, 128.1, 127.8, 125.7, 119.4, 113.9, 81.5, 76.5, 75.3, 73.8, 73.7, 73.4, 73.2, 70.7, 68.6, 67.3 ; CH_0 δ 172.3, 172.2, 167.0, 159.3, 151.5, 144.7, 138.1, 131.1, 103.4, 45.3; IR (neat) 2930, 1725, 1513, 1459, 1377, 1246, 1156, 1088, 1044, 824, 742,

644, 590, 535 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{64}H_{96}O_{15}NaSi$ (M+Na) 1155.6416, found 1155.6415.

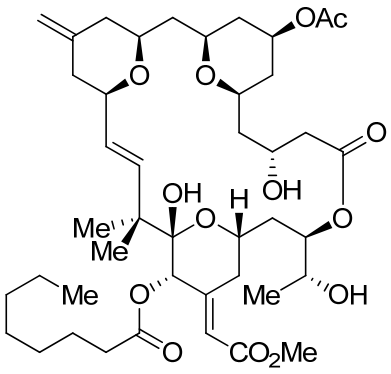


Preparation of Protected (1*S*,3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*,21*R*,23*R*,25*S*)-25-acetoxy-17-((*R*)-1-((benzyloxy)methoxy)ethyl)-11-methoxy-13-(2-methoxy-2-oxoethylidene)-21-((4-methoxybenzyl)oxy)-10,10-dimethyl-5-methylene-19-oxo-18,27,28,29-tetraoxatetra cyclo [21.3.1.13,7.111,15]nonacos-8-en-12-yl octanoate (2.75): To a stirring solution of TES ether **2.74** (2.0 mg, 0.0018 mmol, 1.0 equiv) in 9:1 THF/pyridine (272 μL, 0.0067 M) in a 4 mL plastic vial was added HF·py (20 %, 108 μL). The solution was stirred at rt for 48 h, then diluted with 50 % EtOAc/hexanes (50 mL), and washed with brine (3 × 5 mL). The solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was carried into the next step without further purification.

To a stirring solution of the aforementioned alcohol in CH_2Cl_2 (352 μL, 0.005 M) in a 4 mL reaction vial at rt were added pyridine (7.0 mg, 0.088 mmol, 50 equiv), 4-dimethylaminopyridine (2.2 mg, 0.018 mmol) and Ac_2O (5.4 mg, 0.053 mmol, 30 equiv). The mixture was stirred at rt overnight, and then diluted with CH_2Cl_2 (1 mL) and quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL). The mixture

was then partitioned between 10 mL of CH_2Cl_2 and 5 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash chromatography with a 1 × 9 cm silica gel column, eluting with 50% EtOAc/hexanes, collecting 12 × 75 mm test tube fractions. The product containing fractions (4-7) were combined and concentrated under reduced pressure to provide pure product **2.75** (1.8 mg, 95% over 2 steps) as a colorless oil: R_f = 0.45 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = +13 (*c* = 0.080, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.39-7.28 (m, 5H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.22 (d, *J* = 15.6 Hz, 1H), 5.95 (d, *J* = 1.5 Hz, 1H), 5.58 (ddd, *J* = 11.7, 4.4, 2.4 Hz, 1H), 5.34 (dd, *J* = 15.6, 8.8 Hz, 1H), 5.18 (s, 1H), 4.86-4.80 (m, 3H), 4.77 (d, *J* = 7.3 Hz, 2H), 4.66 (ABq, *J* = 11.7 Hz, Δν = 18.0 Hz, 2H), 4.48 (ABq, *J* = 10.7 Hz, Δν = 18.0 Hz, 2H), 4.47 (d, *J* = 10.7 Hz, 1H), 4.22-4.16 (m, 1H), 3.99-3.92 (m, 2H), 3.76 (s, 3H), 3.73-3.66 (m, 5H), 3.52-3.40 (m, 2H), 3.18 (t, *J* = 10.7 Hz, 1H), 3.08 (s, 3H), 2.52 (dd, *J* = 11.6, 3.4 Hz, 1H), 2.47 (dd, *J* = 15.6, 9.3 Hz, 1H), 2.32-2.26 (m, 3H), 2.20 (d, *J* = 13.2 Hz, 1H), 2.13-2.07 (m, 2H), 2.05 (s, 3H), 1.99 (d, *J* = 14.7 Hz, 1H), 1.94 (d, *J* = 11.7 Hz, 1H), 1.64-1.50 (m, 3H), 1.46-1.38 (m, 1H), 1.34-1.22 (m, 10H), 1.09 (s, 6H), 1.07 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.2, 171.3, 170.7, 167.0, 159.3, 151.5, 144.4, 141.7, 138.1, 130.9, 129.6, 128.6, 128.1, 127.9, 125.7, 119.4, 113.9, 109.1, 103.4, 93.7, 81.5, 76.3, 74.8, 73.7, 73.5, 73.3, 73.2, 72.3, 70.8, 70.4, 69.8, 67.3, 55.5, 52.8, 51.4, 45.2, 44.0, 42.9, 41.9, 41.4, 41.0, 37.6, 34.8, 34.8, 31.9, 31.0, 29.9, 29.2, 29.1, 26.5, 24.9, 22.8, 21.5, 20.2, 15.3, 14.3; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 52.8, 51.4, 26.5, 21.5, 20.2, 15.3, 14.3; CH_2 δ 109.1, 93.7, 72.3, 69.8, 44.0, 42.9, 41.9, 41.4, 41.0,

37.6, 34.8, 34.8, 31.9, 31.0, 29.9, 29.2, 29.1, 24.9, 22.8; CH δ 141.7, 129.6, 128.6, 128.1, 127.9, 125.7, 119.4, 113.9, 81.5, 76.3, 74.8, 73.7, 73.5, 73.3, 73.2, 70.8, 70.4, 67.3; CH_0 δ 172.2, 171.3, 170.7, 167.0, 159.3, 151.5, 144.4, 138.1, 130.9, 103.4, 45.2; IR (neat) 2929, 2856, 1665, 1613, 1514, 1436, 1377, 1309, 1243, 1158, 1091, 1040, 892, 815, 753, 699, 536 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{60}H_{84}O_{16}Na$ (M+Na) 1083.5657, found 1083.5643.

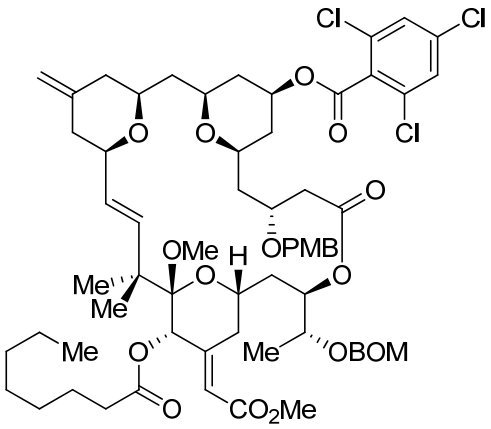


Preparation of (1*S*,3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*,21*R*,23*R*,25*S*)-25-acetoxy-11,21-dihydroxy-17-((*R*)-1-hydroxyethyl)-13-(2-methoxy-2-oxoethylidene)-10,10-dimethyl-5-methylene-19-oxo-18,27,28,29-tetraoxatetracyclo[21.3.1.13,7.111,15]nonacos-8-en-12-yl octanoate (Merle 27). To a stirring solution of **1.154** (1.4 mg, 0.0013mmol, 1.0 equiv) in CH_2Cl_2 (0.26 mL, 0.005 M) in a 4 mL reaction vial at 0 ºC were added aqueous pH 7 buffer (0.15 mL) and DDQ (1.5 mg, 0.0068 mmol, 5.0 equiv). The reaction mixture was stirred at 0 ºC for 2 h and additional DDQ (1.5 mg, 0.0068 mmol, 5.0 equiv) was then added. Stirring continued for 1.5 h and the reaction mixture was diluted with CH_2Cl_2 (1 mL) and quenched by addition of saturated aqueous $NaHCO_3$ solution (1 mL). After stirring vigorously for 10 min at rt the mixture was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous phase was separated

and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and then concentrated under reduced pressure. The crude material was taken on to the next step without purification.

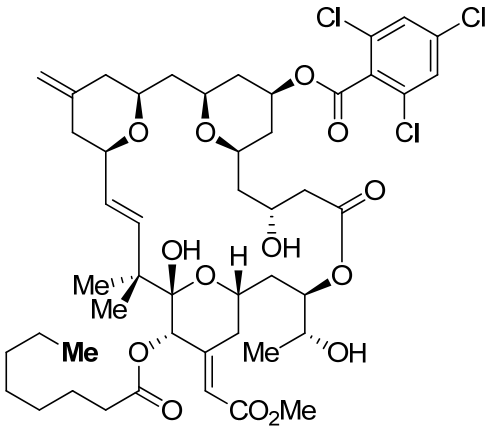
To a 4 mL reaction vial containing the aforementioned analogue precursor was added a $LiBF_4$ in 25:1 CH_3CN/H_2O (238 μL of 0.25 M, 0.059 mmol, 45.0 equiv). The reaction vial was sealed and the mixture was stirred at 80 ºC for 10 h. After cooling to rt, the reaction mixture was diluted with EtOAc (1 mL) and was quenched by the addition of saturated aqueous $NaHCO_3$ solution (0.5 mL). The mixture was partitioned between EtOAc (10 mL) and saturated $NaHCO_3$ aqueous solution (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered and then concentrated under reduced pressure. Purification was accomplished using flash chromatography with a 0.6 × 4 cm silica gel column, eluting with 40% EtOAc/hexanes, collecting 6 × 50 mm test tube fractions. The product containing fractions (4-13) were combined and concentrated under reduced pressure to provide analogue **Merle 27** (0.93 mg, 87% over 2 steps) as a colorless oil: R_f = 0.11 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = +20 (*c* = 0.047, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 5.99 (d, *J* = 2.0 Hz, 1H), 5.79 (d, *J* = 16.1 Hz, 1H), 5.33 (dd, *J* = 15.6, 8.3 Hz, 1H), 5.23 (ddd, *J* = 11.7, 5.9, 2.9 Hz, 1H), 5.13 (s, 1H), 4.90-4.80 (m, 1H), 4.72 (d, *J* = 4.4 Hz, 2H), 4.41 (d, *J* = 12.2 Hz, 1H), 4.23 (t, *J* = 11.7 Hz, 1H), 4.08-4.00 (m, 2H), 3.83 (q, *J* = 6.3 Hz, 1H), 3.73-3.71 (m, 1H), 3.68 (s, 3H), 3.65-3.50 (m, 3H), 2.51 (dd, *J* = 12.2, 2.0 Hz, 1H), 2.45 (t, *J* = 11.7 Hz, 1H), 2.31 (ddd, *J* = 7.8, 3.9, 3.9 Hz, 2H), 2.13-2.06 (m, 2H), 2.06-2.00 (m, 5H), 2.00-1.96 (m, 2H), 1.96-1.92 (m, 6H), 1.78-1.68 (m, 1H), 1.66-1.60 (m, 2H), 1.56-1.48 (m, 2H), 1.36-1.22 (m, 13H), 1.14 (s, 3H),

1.01 (s, 3H), 0.88 (t, J = 7.3 Hz,3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.3, 172.2, 170.7, 167.2, 152.1, 143.9, 139.0, 130.0, 119.9, 108.9, 99.1, 80.2, 77.8, 76.9, 74.4, 73.9, 73.6, 70.5, 69.6, 68.7, 64.7, 51.3, 45.1, 43.1, 42.8, 41.5, 40.0, 37.5, 36.1, 34.9, 31.9, 31.8, 31.5, 29.2, 29.1, 25.0, 24.9, 22.9, 22.8, 21.4, 20.0, 20.0, 4.3; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 51.3, 25.0, 21.4, 20.0, 20.0, 14.3; CH_2 δ 108.9, 43.1, 42.8, 41.5, 40.0, 37.5, 36.1, 34.9, 31.9, 31.8, 31.5, 29.2, 29.1, 24.9, 22.9, 22.8; CH δ 139.0, 130.0, 119.9, 80.2, 77.8, 76.9, 74.4, 73.9, 73.6, 70.5, 69.6, 68.7, 64.7; CH_0 δ 172.3, 172.2, 170.7, 167.2, 152.1, 143.9, 99.1, 45.1; IR (neat) 3583, 3458, 3070, 2955, 2932, 2857, 1734, 1612, 1513, 1472, 1463, 1377, 1250, 1172, 1105, 843, 823, 742, 703, 688 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{43}H_{66}O_{14}Na$ (M+Na) 829.4350, found 829.4372.

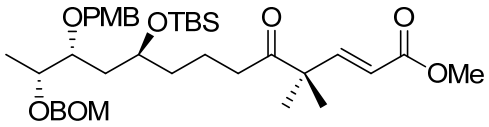


Preparation of (1*S*,3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*,21*R*,23*R*,25*S*)-17-((*R*)-1-((benzyloxy)methoxy)ethyl)-11-methoxy-13-(2-methoxy-2-oxoethylidene)-21-((4-methoxybenzyl)oxy)-10,10-dimethyl-5-methylene-12-(octanoyloxy)-19-oxo-18,27,28,29-tetraoxatetracyclo[21.3.1.13,7.111,15]nonacos-8-en-25-yl-2,4,6-trichlorobenzoate (2.71). Prepared from **2.70** (2.8 mg) in the same manner as **2.73** to provide product **2.71** (2.6 mg, 79 %) as a white film: R_f = 0.20 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +5 (c = 0.10,

$CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.28 (m, 7H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.22 (d, *J* = 15.6 Hz, 1H), 5.93 (d, *J* = 1.0 Hz, 1H), 5.58 (ddd, *J* = 11.7, 4.4, 2.4 Hz, 1H), 5.34 (dd, *J* = 15.6, 8.3 Hz, 1H), 5.20-5.11 (m, 2H), 4.83 (s, 1H), 4.78 (d, *J* = 8.8 Hz, 2H), 4.65 (ABq, *J* = 11.7 Hz, Δν = 19.7 Hz, 2H), 4.50 (d, *J* = 10.7 Hz, Δν = 21.4 Hz, 2H), 4.24-4.15 (m, 1H), 4.00-3.90 (m, 2H), 3.77 (s, 3H), 3.72-3.66 (m, 4H), 3.62 (dd, *J* = 14.2, 7.3 Hz, 1H), 3.54-3.46 (m, 2H), 3.24 (t, *J* = 11.3 Hz, 1H), 3.06 (s, 3H), 2.50 (d, *J* = 6.9 Hz, 2H), 2.33-2.23 (m, 3H), 2.20 (d, *J* = 12.7 Hz, 1H), 2.13-1.95 (m, 6H), 1.90-1.81 (m, 2H), 1.80-1.75 (m, 1H), 1.65-1.50 (m, 6H), 1.34-1.20 (m, 10H), 1.10 (s, 6H), 1.08 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); 125 MHz NMR ($CDCl_3$) δ 172.2, 172.1, 167.0, 164.9, 159.3, 151.5, 144.4, 141.7, 138.1, 134.7, 133.2, 132.3, 130.9, 129.9, 129.8, 129.6, 128.6, 128.1, 127.9, 127.8, 125.8, 119.5, 113.9, 109.1, 103.4, 93.7, 81.5, 76.3, 74.6, 73.7, 73.5, 73.3, 73.2, 72.3, 71.5, 70.9, 69.8, 67.3, 55.5, 52.8, 51.4, 45.3, 44.0, 42.9, 42.0, 41.5, 41.0, 37.3, 34.8, 31.9, 31.1, 29.9, 29.2, 26.5, 24.9, 22.8, 20.3, 15.4, 14.3; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 52.8, 51.4, 26.5, 15.3, 14.3; CH_2 δ 109.1, 93.7, 72.3, 69.8, 44.0, 42.9, 42.0, 41.5, 41.0, 37.3, 34.8, 31.9, 31.1, 29.9, 29.2, 29.1, 24.9, 22.8, 20.3; CH δ 141.7, 129.6, 128.6, 128.1, 127.9, 127.9, 125.8, 119.5, 113.9, 81.5, 76.3, 74.6, 73.7, 73.5, 73.3, 73.2, 71.5, 70.9, 67.3; CH_0 δ 172.2, 172.1, 167.0, 164.9, 159.3, 151.5, 144.4, 138.1, 134.7, 133.2, 132.3, 130.9, 129.9, 129.8, 103.4, 45.3; IR (neat) 2926, 2853, 1738, 1651, 1580, 1548, 1514, 1435, 1382, 1249, 1160, 1103, 1042, 819, 668, 541 cm^{-1}; LRMS (EI) Calcd for $C_{65}H_{83}Cl_3O_{16}Na$ (M+Na): 1247.5, Found: 1247.5.



Preparation of (1*S*,3*S*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*,21*R*,23*R*,25*S*)-11,21-dihydroxy-17-((*R*)-1-hydroxyethyl)-13-(2-methoxy-2-oxoethylidene)-10,10-dimethyl-5-methylene-12-(octanoyloxy)-19-oxo-18,27,28,29-tetraoxatetracyclo[21.3.1.13,7.111,15]nonacos-8-en-25-yl 2,4,6-trichlorobenzoate (2.72). Prepared from **2.71** (2.6 mg) in the same manner as Merle 27 to provide the analogue **2.72** (1.3 mg, 63 %) as a white film: R_f = 0.45 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = +3 (*c* = 0.065, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.35-7.40 (m, 2H), 5.99 (s, 1H), 5.79 (d, *J* = 15.6 Hz, 1H), 5.33 (dd, *J* = 16.1, 8.8 Hz, 1H), 5.22 (m, 1H), 5.14 (s, 1H), 4.76-4.70 (m, 3H), 4.40 (d, *J* = 12.2 Hz, 1H), 4.27-4.20 (m, 1H), 4.07-4.00 (m, 2H), 3.85-3.80 (m, 1H), 3.73-3.70 (m, 1H), 3.68 (s, 3H), 3.62-3.55 (m, 3H), 2.54 (d, *J* = 12.2 Hz,1H), 2.47 (d, *J* = 11.7 Hz, 1H), 2.31 (ddd, *J* = 3.4, 7.3, 7.3 Hz, 2H), 2.18-1.80 (m, 12H), 1.66-1.40 (m, 5H), 1.32-1.22 (m, 13H), 1.14 (s, 3H), 1.04 (s, 3H), 0.88(t, *J* = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.4, 172.2, 167.2, 163.6, 159.7, 152.1, 143.8, 139.0, 132.7, 129.9, 128.3, 119.9, 108.9, 99.1, 95.0, 80.2, 77.8, 77.4, 74.4, 73.9, 73.6, 72.0, 70.5, 68.7, 64.7, 51.3, 45.1, 43.1, 42.8, 42.3, 41.6, 40.0, 37.1, 36.7, 36.1, 34.9, 31.9, 31.5, 29.3, 29.1, 25.0, 24.9, 22.8, 20.1, 20.0, 14.3; IR (neat) 3458, 2933, 2859, 1732, 1611, 1513, 1466, 1428, 1376, 1250, 1172, 1106, 843, 742, 704, 613 cm^{-1}. LRMS (EI) Calcd for $C_{48}H_{65}Cl_3O_{14}Na$ (M+Na): 993.3, Found: 993.3.

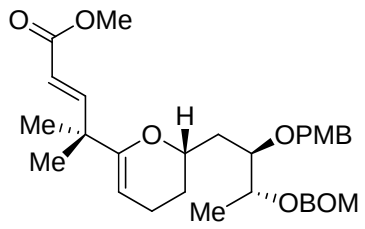


Preparation of (9*S*,11*R*,12*R*,*E*)-methyl-12-(benzyloxymethoxy)-9-(*tert*-butyl dimethylsilyloxy)-11-(4-methoxybenzyloxy)-4,4-dimethyl-5-oxotridec-2-enoate (2.100). To a stirring solution of alkene **2.25** (761.1 mg, 1.242 mmol, 1.0 equiv) in 5% methanol/EtOAc (50 mL) in a 100 mL rb flask at -78 °C was added $NaHCO_3$ (1.043 g, 12.42 mmol, 10.0 equiv). A steady stream of O_3 was bubbled through the reaction mixture until a light blue color developed. The excess O_3 was removed by bubbling O_2 through the mixture for 15 min until the light blue color faded. PPh_3 (325.8 mg, 1.863 mmol, 1.5 equiv) was added in one portion, and the reaction mixture was slowly warmed to rt, and stirred for 12 h. The solids were removed via filtration, and the filtrate was concentrated under reduced pressure. The resulting yellow oil was taken up in 10% Et_2O/ pentane (200 mL) in a 500 mL rb flask, and placed in a -20 °C freezer for 6 h. The triphenylphosphine oxide precipitate was removed via filtration, and rinsed with 100 mL of ice cold 1% Et_2O/pentane. The solvent was removed under reduced pressure to yield the crude aldehyde as a light yellow oil, which was taken on to the next step without further purification.

To a stirring solution of methyl diethyl phosphonoacetate (574.3 mg, 2.732 mmol, 2.2 equiv) in THF (15 mL) in a 100 mL rb flask at 0 °C, was added NaH (65.6 mg, 2.732 mmol, 2.2 equiv) portionwise over 10 min. The reaction mixture was stirred at 0 °C for 30 min, and then a solution of the aforementioned crude aldehyde in THF (5 mL) was added to the mixture slowly via cannula. The transfer was completed with two 2.5 mL

rinses using THF. The reaction mixture was stirred at 0 °C for an additional 2 h, then quenched by the addition of saturated aqueous NH_4Cl solution (25 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried with Na_2SO_4, filtered and then concentrated under reduced pressure. Purification was accomplished using flash chromatography on a 3 × 20 cm silica gel column, eluting with 15% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (9-20) were combined and concentrated under reduced pressure to give the product **2.100** (781.5mg, 94% over 2 steps) as a colorless oil: R_f = 0.40 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +27.9 (*c* = 0.405, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.33 (m, 4H), 7.33-7.28 (m, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 15.6 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.89 (d, *J* = 15.6 Hz, 1H), 4.81 (ddd, *J* = 7.3, 6.8, 6.4 Hz, 2H), 4.63 (q, *J* = 11.7 Hz, 2H), 4.59 (d, *J* = 11.2 Hz, 1H), 4.45 (d, *J* = 10.7 Hz, 1H), 4.02 (dd, *J* = 16.4, 14.9 Hz, 1H), 3.89 (dddd, *J* = 8.8, 8.8, 5.4 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 3.64 (ddd, *J* = 9.4, 4.4, 2.4 Hz, 1H), 2.42 (ddd, *J* = 7.3, 7.3, 2.0 Hz, 2H), 1.69 (ddd, *J* = 14.2, 8.8, 2.4 Hz, 1H), 1.62-1.54 (m, 3H), 1.47-1.40 (m, 2H), 1.27 (s, 6H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) 210.8, 166.9, 159.2, 152.0, 138.1, 131.1, 129.3, 128.6, 128.0, 127.8, 120.5, 113.9, 93.4, 78.2, 73.0, 72.1, 69.6, 69.5, 55.4, 51.9, 50.7, 38.5, 37.8, 37.4, 26.1, 23.7, 19.2, 18.3, 15.2, -3.5, -4.2; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 51.9, 26.1, 23.7, 15.2, -3.6, -4.2; CH_2 δ 93.4, 72.1, 69.5, 38.5, 37.8, 37.4, 19.2; CH δ 152.0, 129.3, 128.6, 128.0, 127.8, 120.5, 113.9, 78.2, 73.0, 69.6; CH_0 δ 210.8, 166.9, 159.2, 138.1, 131.1, 50.7, 18.3; IR (neat) 2953, 1725, 1648, 1613, 1513, 1463, 1382, 1300, 1249, 1174, 1040,

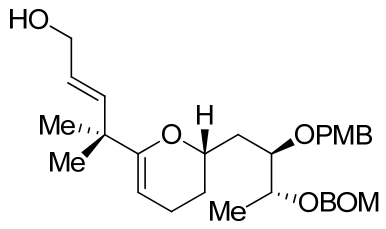
834, 774, 737, 698, 590, 536 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{38}H_{58}NaO_8Si$ (M+Na) 693.3799, found 693.3795.



Preparation of (*E*)-methyl 4-((*S*)-2-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-3,4-dihydro-2H-pyran-6-yl)-4-methylpent-2-enoate (2.101). To a stirring solution of silyl ether **2.100** (769.2 mg, 1.146 mmol, 1.0 equiv) in 20:1 CH_3CN/ H_2O (23 mL) in a 50 mL high density polyethylene bottle at 0 °C were added pyridine (3.8 mL) and a 48% aqueous HF solution (0.5 mL). The solution was stirred at 0 °C for 30 min, and then warmed to rt. After 30 min of stirring at rt, an additional 0.5 mL of aqueous HF solution (48%) was added every hour until TLC analysis indicated complete consumption of the starting material. The reaction mixture was quenched by slowly pipetting the solution into a mixture of saturated aqueous $NaHCO_3$ solution (50 mL) and EtOAc (50 mL). Then solid $NaHCO_3$ was added until effervescence was complete. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with saturated aqueous $CuSO_4$ solution (2 × 20 mL), and brine (2 × 20 mL). The solution was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude intermediate alcohol as a light yellow oil. This intermediate was carried on to the next step without further purification.

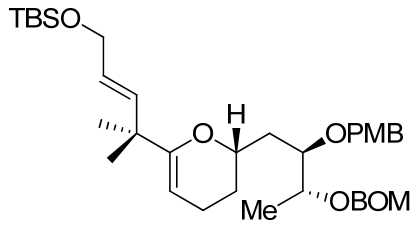
To a stirring solution of the aforementioned crude alcohol in benzene (23 mL) in a 50 mL rb flask equipped with a condenser and a Dean-Stark trap was added CSA (26.6 mg, 0.115 mmol, 0.1 equiv). The solution was heated at reflux for 1 h, and then cool to rt. The reaction mixture was quenched with by the addition of pyridine (0.1 mL), and the solvent was removed under reduced pressure. Purification was accomplished using flash chromatography on a 3.0 × 17 cm silica gel column, eluting with 10% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (10-22) were combined and concentrated under reduced pressure to give the product dihydropyran **2.101** (553.7 mg, 90% over 2 steps) as a colorless oil: R_f = 0.42 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +54.6 (*c* = 0.455, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.37-7.34 (m, 4H), 7.33-7.29 (m, 1H), 7.26 (d, J = 8.8 Hz, 2H), 7.07 (d, *J* = 15.6 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.84 (d, *J* = 16.1 Hz, 1H), 4.83 (d, *J* = 2.9 Hz, 2H), 4.65 (d, *J* = 2.9 Hz, 2H), 4.62 (d, *J* = 10.7 Hz, 1H), 4.63-4.61 (m, 1H), 4.50 (d, *J* = 10.7 Hz, 1H), 4.05-3.99 (m, 1H), 3.97 (dd, *J* = 6.5, 5.4 Hz, 1H), 3.82 (dd, *J* = 5.4, 2.0 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 2.14-2.06 (m, 1H), 2.04-1.96 (m, 1H), 1.84-1.74 (m, 2H), 1.62 (ddd, *J* = 14.2,10.7, 2.4 Hz, 1H), 1.52 (dddd, *J* = 13.2, 9.8, 9.8, 5.9 Hz, 1H), 1.24 (s, 3H), 1.22 (s, 3H), 1.21 (d, *J* = 6.4 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) 167.6, 159.4, 157.2, 156.4, 138.2, 131.1, 129.6, 128.6, 128.0, 127.8, 118.0, 114.0, 94.5, 93.6, 77.7, 73.9, 73.6, 72.0, 69.5, 55.4, 51.5, 41.4, 36.2, 28.2, 25.3, 25.2, 20.5, 15.6; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 51.5, 25.3, 25.2, 15.6; CH_2 δ 93.6, 73.6, 69.5, 36.2, 28.2, 20.5; CH δ 156.4, 129.6, 128.6, 128.0, 127.8, 118.0, 114.0, 94.5, 77.7, 73.9, 72.0; CH_0 δ 167.6, 159.4, 157.2, 138.2, 131.1, 41.4; IR (neat) 2949, 1723, 1659, 1613, 1586, 1513, 1456, 1381, 1294,

1248, 1175, 1095, 1039, 821, 737, 699, 588 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{32}H_{42}NaO_7$ (M+Na) 561.2828, found 561.2845.



Preparation of (*E*)-4-((*S*)-2-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(4-methoxy benzyloxy)butyl)-3,4-dihydro-2H-pyran-6-yl)-4-methylpent-2-en-1-ol (2.102). To a stirring solution of ester **2.101** (200.6 mg, 0.3724 mmol, 1.0 equiv) in CH_2Cl_2 (7.5 mL, 0.05 M) at -78 °C was added a solution of diisobutylaluminium hydride (782 μL of 1.0 M, 0.7820 mmol, 2.1 equiv) in CH_2Cl_2 slowly via syringe. The solution was stirred at -78 °C for 2 h, then warmed to 0 °C and stirred for 0.5 h. The reaction was quenched by the addition of EtOAc (0.5 mL) and the mixture was stirred at 0 °C for 10 min. A saturated Rochelle salt solution (10 mL) was added. Then the aqueous phase was separated and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash chromatography on a 3 × 14 cm silica gel column, eluting with 30% EtOAc/hexanes (500mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (6-12) were combined and concentrated under reduced pressure to give the product alcohol **2.102** (171.6 mg, 90%) as a clear colorless oil: R_f = 0.27 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +40.7 (*c* = 0.945, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.34 (m, 4H), 7.32-7.28 (m, 1H), 7.26 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.77 (d, *J* = 16.1 Hz, 1H), 5.62 (ddd, *J* = 15.6, 5.9, 5.9 Hz, 1H), 4.84 (s, 2H), 4.65 (s, 2H), 4.62

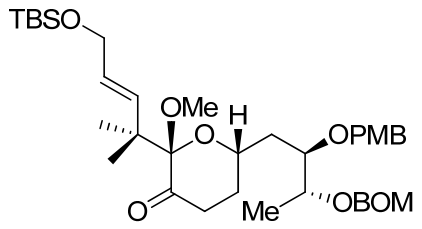
(d, *J* = 10.7 Hz,1H), 4.57 (d, *J* = 3.7 Hz, 1H), 4.53 (d, *J* = 10.7 Hz, 1H), 4.06 (d, *J* = 5.4 Hz, 2H), 4.03-3.94 (m, 2H), 3.85 (ddd, *J* = 10.3, 4.9, 2.4 Hz, 1H), 3.80 (s, 3H), 2.09 (dddd, *J* = 16.6, 9.8, 6.8, 2.9 Hz, 1H), 2.03-1.96 (m, 1H), 1.83 (ddd, *J* = 14.2, 10.7, 2.0 Hz, 1H), 1.77 (ddd, *J* = 13.7, 6.4, 3.4Hz, 1H), 1.60 (ddd, *J* = 14.2, 10.3, 2.4 Hz, 1H), 1.55-1.46 (m, 1H), 1.20 (d, *J* =6.4 Hz, 3H), 1.18 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) 159.4, 158.9, 140.5, 138.1, 131.2, 129.6, 128.6, 128.1, 127.9, 125.8, 114.1, 93.6, 93.3, 78.0, 74.2, 73.4, 71.8, 69.7, 64.1, 55.5, 40.7, 36.1, 28.3, 26.1, 26.0, 20.5, 15.7; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 26.1, 26.0, 15.7; CH_2 δ 93.3, 73.4, 69.7, 64.1, 36.1, 28.3, 20.5; CH δ 140.5, 129.6, 128.6, 128.1, 127.9, 125.8, 114.1, 93.3, 78.0, 74.2, 71.8; CH_0 δ 159.4, 158.9, 138.1, 131.2, 40.7; IR (neat) 3452 (b), 3031, 2933, 1661, 1612, 1586, 1513, 1457, 1381, 1296, 1248, 1174, 1151, 1039, 977, 821, 740, 698 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{31}H_{42}NaO_6$ (M+Na) 533.2879, found 533.2874.



Preparation of ((*E*)-4-((*S*)-2-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(4-methoxy benzyloxy) butyl)-3,4-dihydro-2H-pyran-6-yl)-4-methylpent-2-enyloxy)(*tert*-butyl) dimethylsilane (2.103). To a stirring solution of alcohol **2.102** (141.5 mg, 0.2771 mmol, 1.0 equiv) in CH_2Cl_2 (5.5 mL, 0.05M) in a 25 mL rb flask at 0 °C were added 2,6-lutidine (178.2 mg, 1.663 mmol, 6.0 equiv) and *tert*-butyldimethylsilyl triflate (183.1 mg, 0.6927 mmol, 2.5 equiv) via syringe. The solution was stirred at 0 °C for 1h, then quenched by the addition of methanol (0.1 mL). After 5 min at 0°C, the mixture was transferred to a

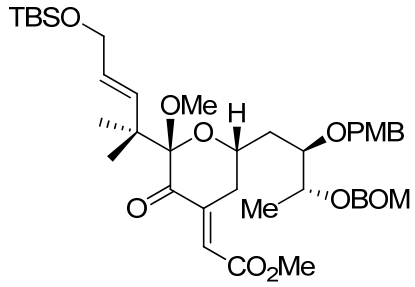
separatory funnel containing saturated $NaHCO_3$ aqueous solution (10 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash chromatography on a 3 × 15 cm silica gel column, eluting with 10% EtOAc/hexanes (500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (5-7) were combined and concentrated under reduced pressure to give the product **2.103** (173.0 mg, quant. yield) as a colorless oil: R_f = 0.25 (10% EtOAc/hexanes); $[\alpha]_D^{20}$ = +38.4 (*c* = 0.475, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.35 (m, 4H), 7.34-7.29 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.77 (ddd, *J* = 15.6, 1.5,1.5 Hz, 1H), 5.54 (ddd, *J* = 15.6, 5.4, 5.4 Hz, 1H), 4.85 (d, *J* = 2.4 Hz, 2H), 4.66 (d, *J* = 3.9 Hz, 2H), 4.64 (d, *J* = 10.8 Hz, 1H), 4.57 (dd, *J* = 4.4, 2.9 Hz, 1H), 4.53 (d, *J* = 10.7 Hz, 1H), 4.15 (dd, *J* = 5.4, 1.5 Hz, 2H), 4.03 (dddd, *J* = 9.8, 9.8, 2.4, 2.4 Hz, 1H), 3.97 (ddd, *J* = 11.2, 6.4, 6.4, Hz, 1H), 3.85 (ddd, *J* = 10.3, 2.0, 2.0 Hz, 1H), 3.80 (s, 3H), 2.09 (dddd, *J* = 17.1, 9.8, 6.8, 2.9 Hz, 1H), 2.02-1.95 (m, 1H), 1.82 (ddd, *J* = 14.1, 10.7, 2.4 Hz, 1H), 1.77 (ddd, *J* = 13.2, 7.4, 2.9 Hz, 1H), 1.63 (ddd, *J* = 14.2, 10.8, 2.4 Hz, 1H), 1.51 (dddd, *J* = 13.2, 9.8, 9.8 5.9 Hz, 1H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 0.92 (s, 9H), 0.07 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$) 159.3, 159.1, 138.7, 138.1, 131.1, 129.6, 128.6, 128.0, 127.8, 125.9, 114.0, 93.6, 93.2, 78.0, 74.1, 73.6, 71.7, 69.6, 64.6, 55.5, 40.5, 36.4, 28.3, 26.2, 26.1, 25.9, 20.6, 18.6, 15.8, -4.8; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.5, 26.2, 26.1, 25.9, 15.8, -4.8; CH_2 δ 93.6, 73.6, 69.6, 64.6, 36.4, 28.3, 20.6; CH δ 138.7, 129.6, 128.6, 128.0, 127.8, 125.9, 114.0, 93.2, 78.0, 74.1, 71.7; CH_0 δ 159.3, 159.1, 138.1, 131.1, 40.5, 18.6; IR (neat) 2930, 2856,

1661, 1581, 1462, 1381, 1249, 1098, 1042, 837, 776 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{37}H_{56}NaO_6Si$ (M+Na) 647.3744, found 647.3754.



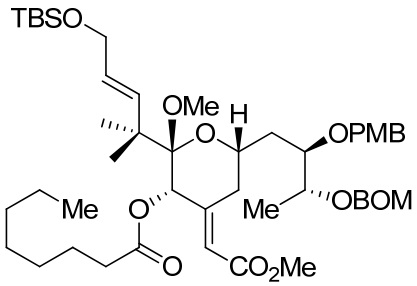
Preparation of (2*S*,6*S*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(4-methoxy benzyloxy)butyl)-2-((*E*)-5-(tert-butyldimethylsilyloxy)-2-methylpent-3-en-2-yl)-2-methoxydihydro-2H-pyran-3(4H)-one (2.93). To a stirring solution of dihydropyran **2.103** (92.7 mg, 0.148 mmol, 1.0 equiv) in CH_2Cl_2 (2.9 mL) in a 15 mL rb flask at -15 °C was added methanol (0.4 mL). The solution was stirred at -15 °C for 5 min, then a solution of purified *m*CPBA (48.6 mg, 0.282 mmol, 1.9 equiv) in methanol (240 μL) was added dropwise via syringe. The syringe was rinsed with an additional 200 μL of methanol and and the resulting solution was added into the reaction mixture. The solution was stirred at -15 °C for 1.5 h, and then warmed to 0 °C and stirred for an additional 30 min. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL) followed by saturated aqueous $NaHSO_3$ solution (2 mL). The mixture was stirred at rt for 10 min until effervescence was complete. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried with Na_2SO_4, filtered, and then concentrated under reduced pressure to provide the crude intermediate alcohol as a colorless oil which was carried on to the next step without further purification.

To a stirring solution of the aforementioned crude alcohol in CH_2Cl_2 (3.0 mL) in a 25 mL rb flask at rt were added 4 Å molecular sieves (100 mg), tetrapropylammonium perruthenate (5.2 mg, 0.0148 mmol, 0.1 equiv) and 4-methylmorpholine-N-oxide (52.1 mg, 0.445 mmol, 3.0 equiv). The mixture was stirred at rt for 1 h. The purification was accomplished by flash chromatography on a 3 × 12 cm flash chromatography, eluting with 15% EtOAc/hexanes (500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (5-7) were combined and concentrated under reduced pressure to give the product ketone **2.93** (78.4 mg, 79% over 2 steps) as a colorless oil: R_f = 0.47 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +25 (*c* = 0.24, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ; 7.38-7.30 (m, 5H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.97 (dt, *J* = 15.6, 1.5 Hz, 1H), 5.50 (dt, *J* = 16.1, 4.9 Hz,1H), 4.85 (ABq, *J* = 7.3 Hz, Δν = 7.8 Hz, 2H), 4.67 (s, 2H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.15 (dd, *J* = 4.9, 1.5 Hz, 2H), 3.89 (ddd, *J* = 12.2, 4.9, 2.0 Hz, 1H), 3.81-3.79 (m, 1H), 3.79 (s, 3H), 3.24 (s, 3H), 2.45 (dd, *J* = 5.4, 1.0 Hz, 1H), 2.42 (d, *J* = 5.4 Hz, 1H), 2.00-1.86 (m, 3H), 1.66 (ddd, *J* = 13.2, 10.3, 2.4 Hz, 1H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.44 (s, 3H), 1.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$); 207.7, 159.4, 138.0, 136.2, 130.8, 129.4, 128.7, 128.0, 127.9, 127.8, 114.0, 104.3, 93.6, 77.3, 72.6, 72.2, 70.2, 69.7, 64.2, 55.5, 52.3, 44.1, 37.7, 36.4, 30.2, 26.2, 23.0, 22.2, 18.6 14.9, -5.0; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.5, 52.3, 26.2, 23.0, 22.2, 14.9, -5.0; CH_2 δ 93.6, 72.2, 69.7, 64.2, 37.7, 36.4, 30.2; CH δ 136.2, 129.4, 128.7, 128.0, 127.9, 127.8, 114.0, 77.3, 72.6, 70.2; CH_0 δ 207.7, 159.4, 138.0, 130.8, 104.3, 44.1, 18.6; IR (neat); 2952, 2931, 2885, 2856, 1724, 1612, 1585, 1513, 1489, 1471, 1382, 1361, 1249, 1174, 1112, 1042, 836, 776, 735, 698, 585 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{38}H_{58}NaO_8Si$ (M+Na) 693.3799, found 693.3798.



Preparation of (*E*)-methyl 2-((2*S*,6*S*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(4-methoxy benzyloxy)butyl)-2-((*E*)-5-(tert-butyldimethylsilyloxy)-2-methylpent-3-en-2-yl)-2-methoxy-3-oxo-2H-pyran-4(3H,5H,6H)-ylidene)acetate (2.104). To a stirring solution of ketone **2.93**(56.3 mg, 0.0839 mmol, 1.0 equiv) in methanol (0.84 mL, 0.1 M) at rt was added K_2CO_3 (63.8 mg, 0.462 mmol, 5.5 equiv) in one portion. A solution of freshly prepared methyl glyoxylate solution in THF (0.987 mL of 1.7 M, 1.678 mmol, 20.0 equiv) wad added via syringe. The mixture was stirred at rt for 1 h, and then diluted with Et_2O (10 mL) and quenched by the addition of saturated aqueous NH_4Cl solution (10 mL). The aqueous phase was separated and extracted with Et_2O (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash chromatography on a 3 × 14 cm column, eluting with 15% EtOAc/hexanes (500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (8-10) were combined and concentrated under reduced pressure to give the product **2.104** (45.2 mg, 73%) as a yellow oil: R_f = 0.48 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -49 (*c* = 0.195, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ; 7.37-7.35 (m, 4H), 7.34-7.30 (m, 1H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.54 (dd, *J* = 3.4, 2.0 Hz, 1H), 5.81 (ddd, *J* = 15.6, 1.5, 1.5 Hz, 1H), 5.41 (ddd, *J* = 16.1, 5.4, 5.4 Hz, 1H), 4.85 (dd, *J* = 12.2, 6.8 Hz, 2H), 4.67 (s, 2H), 4.61 (d, *J* = 10. 7 Hz, 1H), 4.41 (d, *J* = 10.7 Hz, 1h), 4.17-4.08 (m, 2H), 4.06 (dd, *J* = 9.3, 2.0 Hz,

1H), 3.90 (ddd, *J* = 10.3, 4.4, 2.0 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.31 (ddd, *J* = 18.6, 2.0, 2.0 Hz, 1H), 3.20 (s, 3H), 2.86 (ddd, *J* = 18.6, 12.2, 3.4 Hz, 1H), 1.97 (ddd, *J* = 14.7, 9.3, 2.0 Hz, 1H), 1.75 (ddd, *J* = 14.7, 9.8, 2.4 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 0.90 (s, 9H), 0.04 (s, 6H); 125 MHz ^{13}C NMR ($CDCl_3$); 197.7, 166.2, 159.3, 148.2, 138.0, 134.8, 130.6, 129.3, 128.7, 128.6, 128.0, 127.9, 122.7, 114.0, 93.6, 76.9, 72.3, 71.7, 69.7, 69.5, 64.1, 55.4, 52.2, 51.9, 44.6, 36.1, 36.1, 26.1, 22.5, 22.0, 14.7, -5.0 ; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 52.2, 26.1, 22.5, 22.0, 14.7, -5.0; CH_2 δ 93.6, 71.7, 69.7, 64.1, 36.1, 36.1; CH δ 134.8, 129.3, 128.7, 128.6, 128.0, 127.9, 122.7, 114.0, 76.9, 72.3, 69.5; CH_0 δ 197.7, 166.2, 159.3, 148.2, 138.0, 130.6, 44.6; IR (neat); 2933, 2857, 1724, 1706, 1613, 1513, 1462, 1382, 1250, 1205, 1177, 1108, 1043, 938, 835, 777, 738, 698, 590, 536 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{41}H_{60}NaO_{10}Si$ (M+Na) 763.3853, found 763.3856.

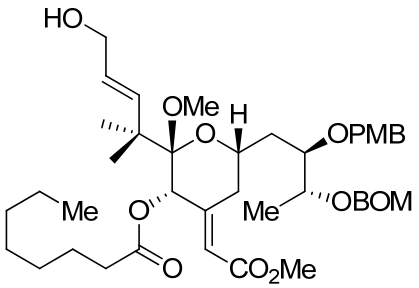


Preparation of (2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((4-methoxybenzyl)oxy)butyl)-2-((*E*)-5-((tert-butyldimethylsilyl)oxy)-2-methylpent-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2H-pyran-3-yloctanoate (2.105). To a stirring solution of ketone **2.104** (41.2 mg, 0.0556 mmol, 1.0 equiv) in methanol (1.9 mL, 0.03M) in a 10 mL rb flask at rt was added $CeCl_3 \cdot 7H_2O$ (10.4 mg, 0.0278 mmol, 0.5 equiv). The reaction mixture was stirred at rt until all the $CeCl_3 \cdot 7H_2O$ crystals had

dissolved, then cooled to -40 °C and stirred for 15 min. $NaBH_4$ (4.2 mg, 0.111 mmol, 2.0 equiv) was then added in one portion. The mixture was stirred at -40 °C for 3 h, and then diluted with 40% EtOAc/hexanes (10 mL), and quenched by the addition of saturated aqueous NH_4Cl solution (5.0 mL). The mixture was poured into a separatory funnel with the aid of 40% EtOAc/hexanes (50 mL). The organic phase was separated, washed with H_2O (10 mL) and brine (10 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was used in the next step without further purification.

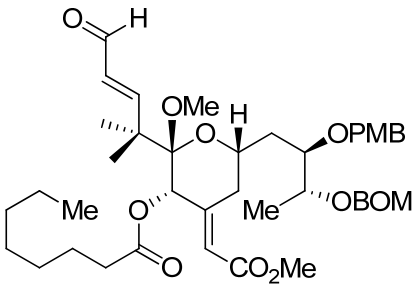
To a stirring solution of the aforementioned crude alcohol in CH_2Cl_2 (2.8 mL, 0.02M) in a 10 mL rb flask at rt, were added pyridine (44.0 mg, 0.556 mmol, 10 equiv), 4-dimethylaminopyridine (13.6 mg, 0.111 mmol, 2.0 equiv), and octanoic anhydride (75.2 mg, 0.278 mmol, 5.0 equiv). The reaction mixture was stirred at rt overnight, then quenched by the addition of methanol (1.0 mL). The mixture was stirred for another 10 min and 10 mL of CH_2Cl_2 was added. The mixture was poured into a separatory funnel containing 10 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 25 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 15 cm silica gel column, eluting with 20% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (11-23) were combined and concentrated under reduced pressure to give the product **2.105** (48.1 mg, quant. yield) as a colorless oil. R_f = 0.34 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = -3.7 (*c* = 0.84, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.30 (m, 5H), 7.21 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.98 (d, *J* = 15.6 Hz,

1H), 5.88 (s, 1H), 5.42 (s, 1H), 5.40 (ddd, *J* = 16.1, 5.3, 5.3 Hz, 1H), 4.86 (ABq, *J* = 6.8 Hz, Δν = 7.0 Hz, 2H), 4.67 (ABq, *J* = 12.2 Hz, Δν = 7.2 Hz, 2H), 4.62 (d, J = 10.7 Hz, 1H0, 4.43 (d, J = 10.8 Hz, 1H), 4.15-4.03 (m, 3H), 3.90 (ddd, J = 10.3, 4.4, 2.0 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.51 (dd, J = 15.6, 2.4 Hz, 1H), 3.23 (s, 3H), 2.36 (t , J = 7.3 Hz, 2H), 2.29 (ddd, J = 7.3, 2.9, 2.9 Hz, 2H), 1.91 (ddd, J = 14.2, 9.8, 2.0 Hz, 1H), 1.73 (ddd, J = 13.7, 10.3, 2.4 Hz, 1H), 1.64 (d, J = 7.3 Hz, 2H), 1.62-1.57 (m, 1H), 1.37-1.26 (m, 10H), 1.23 (d, J = 6.3 Hz, 3H), 1.11 (s, 6H), 0.91 (s, 9H), 0.89 (t, J = 7.3 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 179.8, 172.3, 166.7, 159.4, 152.7, 138.2, 130.7, 129.5, 128.7, 128.0, 127.9, 124.9, 117.5, 114.0, 102.8, 93.5, 77.0, 72.6, 72.1, 72.0, 69.6, 68.4, 64.7, 55.5, 51.7, 51.3, 45.9, 36.5, 34.5, 34.2, 32.8, 31.9, 29.2, 26.2, 24.9, 24.6, 23.7, 22.8, 18.6, 15.0, 14.3, -4.9; 125 MHz DEPT ^{13}C NMR ($CDCl_3$) CH_3 δ 55.5, 51.7, 51.3, 26.2, 24.6, 23.7, 15.0, 14.3; CH_2 δ 93.5, 72.1, 69.6, 64.7, 36.5, 34.5, 34.2, 32.8, 31.9, 29.2, 24.9, 22.8; CH δ 138.2, 129.5, 128.7, 127.9, 117.5, 114.0, 77.0, 72.6, 72.0, 68.4; CH0 δ 179.8, 172.3, 166.7, 159.4, 152.7, 130.7, 102.8, 45.9, 18.6; IR (neat) 2953, 2929, 2856, 1743, 1721, 1665, 1612, 1514 1462, 1435, 1382, 1301, 1249, 1156, 1108, 1044, 836, 776, 737, 687, 576 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{49}H_{76}O_{11}Na$ (M+Na) 891.5055, found 891.5070.



Preparation of (2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((4-methoxybenzyl)oxy) butyl)-2-((*E*)-5-hydroxy-2-methylpent-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene) tetrahydro-2H-pyran-3-yl octanoate (2.106). To a stirring solution of the TBS ether **2.105** (201.2 mg, 0.241 mmol, 1.0 equiv) in a 9:1 THF/ pyridine solution (4.0 mL, 0.06M) at 0 °C in a 25 mL plastic bottle were added methanol (0.4 mL) and 20% HF/Py (1.0 mL). The solution was stirred at 0 °C for 5 min and then warmed to rt. Stirring was continued for 3 h and the reaction mixture was then quenched by pipetting it into a mixture of saturated aqueous $NaHCO_3$ solution (40 mL) and 50% EtOAc/hexanes (40 mL) in a separatory funnel. The aqueous phase was separated and extracted with 50% EtOAc/hexanes (3 × 50 mL). The combined organic phase was dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 15 cm silica gel column, eluting with 20% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (10-22) were combined and concentrated under reduced pressure to give the product **2.106** (164.4 mg, 94% yield) as a colorless oil: R_f = 0.28 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -6 (*c* = 0.23, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.30 (m, 5H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.97 (d, *J* = 15.6 Hz, 1H), 5.88 (s, 1H), 5.50 (ddd, *J* = 15.6, 5.9, 5.9 Hz, 1H), 5.48 (s, 1H), 4.86 (ABq, *J* = 6.8 Hz, Δν = 6.3 Hz, 2H), 4.68 (s, 2H), 4.67-4.61 (m, 1H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.42 (d, *J* = 10.7 Hz, 1H), 4.14 (dd, *J* = 6.4, 4.4, Hz, 1H), 4.10-4.00 (m, 3H), 3.90 (ddd, *J* = 10.3, 4.4, 2.0 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.45 (dd, *J* = 16.1, 2.0 Hz, 1H), 3.23 (s, 3H), 2.38-2.32 (m, 1H), 2.30 (ddd, *J* = 7.3, 7.3, 3.4 Hz, 2H), 1.92 (ddd, *J* = 14.2, 9.8, 2.0 Hz, 1H), 1.73 (ddd, *J* = 14.2, 10.3, 2.4 Hz, 1H), 1.65-1.58 (m, 1H), 1.35 -1.26 (m, 10H), 1.22 (d, *J*

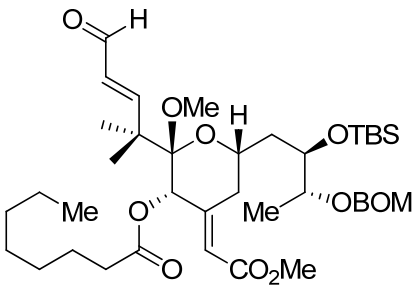
= 6.3 Hz, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 0.89 (t, *J* = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.5, 166.8, 159.4, 152.7, 139.8, 138.1, 130.7, 129.5, 128.7, 128.0, 127.9, 125.3, 117.2, 114.0, 102.7, 93.5, 76.8, 72.4, 72.0, 71.9, 69.7, 68.5, 64.4, 55.5, 51.4 (×2), 46.3, 36.4, 34.7, 33.1, 31.9, 29.2, 29.1, 24.8, 24.3, 24.1, 22.8, 14.8, 14.3; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 51.4 (×2), 24.3, 24.1, 14.8, 14.3; CH_2 δ 93.5, 72.0, 69.7, 36.4, 34.7, 33.1, 31.9, 29.2, 29.1, 24.8, 22.8; CH δ 139.8, 129.5, 128.7, 128.0, 127.9, 125.3, 117.2, 114.0, 76.8, 72.4, 71.9, 68.5; CH0 δ 172.5, 166.8, 159.4, 152.7, 138.1, 130.7, 102.7, 46.3; IR (neat) 2952, 2931, 2857, 1741, 1719, 1663, 1612, 1586, 1462, 1435, 1381, 1301, 1248, 1229, 1155, 1106, 1039, 979, 903, 883, 821, 737, 698 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{43}H_{62}O_{11}Na$ (M+Na) 777.4190, found 777.4191.



Preparation of (2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((4-methoxybenzyl)oxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-2-methyl-5-oxopent-3-en-2-yl)tetrahydro-2H-pyran-3-yl octanoate (2.107). To a stirring solution of alcohol **2.106** (32.8 mg, 0.0434 mmol, 1.0 equiv) in CH_2Cl_2 (4.3 mL, 0.01M) at 0 °C in a 25 mL rb flask were added pyridine (68.7 mg, 0.868 mmol, 20 equiv) and Dess-Martin periodinane (55.3 mg, 0.130 mmol, 3.0 equiv) in one portion. The mixture was stirred at 0 °C for 1 h, and then quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution (1.0 mL). The mixture was stirred until the solution turned clear, then transferred into a

mixture of saturated aqueous $NaHCO_3$ solution (5 mL) and CH_2Cl_2 (20 mL) in a separatory funnel. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 12 cm silica gel column, eluting with 20% EtOAc/hexanes (500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (4-8) were combined and concentrated under reduced pressure to give the product **2.107** (30.1 mg, 92% yield) as a colorless oil. R_f = 0.27 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = -6.2 (c = 0.37, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.29-7.20 (m, 5H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 5.84 (dd, *J* = 16.1, 7.8, 1H), 5.79 (s, 1H), 5.38 (s, 1H), 4.78 (ABq, *J* = 6.8 Hz, Δν = 11.4 Hz, 2H), 4.58 (s, 2H), 4.54 (d, *J* = 11.2 Hz, 1H), 4.31 (d, *J* = 11.2 Hz, 1H), 4.09 (dd, *J* = 6.4, 5.4 Hz, 1H), 4.03 (ddd, *J* = 9.3, 9.3, 2.4 Hz, 1H), 3.81 (ddd, *J* = 10.3, 4.4, 2.0 Hz, 1H), 3.71 (s, 3H), 3.61 (s, 3H), 3.45 (dd, *J* = 16.1, 2.0 Hz, 1H), 3.17 (s, 3H), 2.29 (dd, *J* = 13.2, 12.8 Hz, 1H), 2.08 (ddd, *J* = 16.1, 7.8, 7.8 Hz, 1H), 2.01 (ddd, *J* = 16.1, 7.3, 7.3 Hz, 1H), 1.88 (ddd, *J* = 14.7, 9.8, 2.0 Hz, 1H), 1.70 (ddd, *J* = 14.2, 10.3, 2.9 Hz, 1H), 1.49-1.42 (m, 1H), 1.23-1.12 (m, 10H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.07 (s, 3H), 1.05 (s, 3H), 0.80 (t, *J* = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 194.7, 171.9, 167.1, 166.4, 159.4, 151.6, 137.9, 130.5, 129.5, 128.7, 128.0, 127.9, 127.1, 117.9, 114.0, 102.6, 93.5, 76.6, 72.2, 71.7, 71.2, 69.7, 69.1, 55.5, 51.5, 51.4,47.6, 36.2, 34.6, 32.9, 31.8, 29.1 (×2), 24.7, 23.9, 22.7, 22.0, 14.6, 14.3; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 51.5, 51.4, 23.9, 22.0, 14.6, 14.3; CH_2 δ 93.5, 71.7, 69.7, 36.2, 34.6, 32.9, 31.8, 29.1 (×2), 24.7, 22.7; CH δ 194.7, 167.1, 129.5, 128.7, 128.0, 127.9, 127.1, 117.9, 114.0, 76.6, 72.2, 71.2, 69.1; CH_0 δ 171.9, 166.4, 159.4, 151.6, 137.9, 130.5, 102.6, 47.6;

IR (neat) 3064, 3030, 2952, 2930, 2857, 2724, 1745, 1720, 1687, 1612, 1514, 1455, 1436, 1380, 1301, 1248, 1229, 1155, 1107, 1042, 819, 736, 698 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{43}H_{60}O_{11}Na$ (M+Na) 775.4033, found 775.4047.

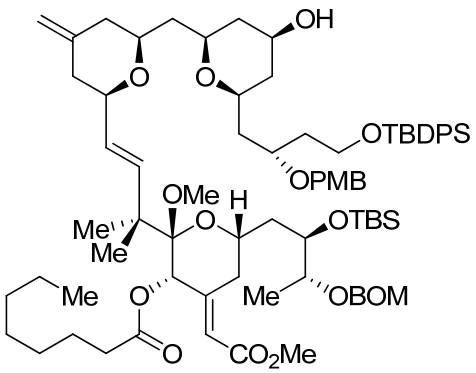


Preparation of (2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((*tert*-butyl dimethylsilyl) oxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-2-methyl-5-oxopent-3-en-2-yl)tetrahydro-2H-pyran-3-yl octanoate (2.92). To a stirring solution of PMB ether **2.107** (77.9 mg, 0.103 mmol, 1.0 equiv) in CH_2Cl_2 (4.0 mL) and *tert*-butyl alcohol (0.2 mL), in a 25 mL rb flask at rt was added aqueous pH 7 buffer solution (0.2 mL). The mixture was cooled to 0 °C and DDQ (47.0 mg, 0.206 mmol, 2.5 equiv) was added in one portion. Stirring was continued at 0 °C for 5 h. The reaction mixture was then quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude intermediate alcohol as a light orange oil. This material was taken on to the next step without further purification.

To a stirring solution of the aforementioned crude alcohol in CH_2Cl_2 (5.1 mL, 0.02M) in a 25 mL rb flask at 0 °C were added 2,6-lutidine (66.2 mg, 0.618 mmol, 6.0 equiv) and *tert*-butyldimethylsilyl triflate (68.1 mg, 0.258 mmol, 2.5 equiv) dropwise via

syringe. The reaction mixture was stirred at 0 °C for 30 min, and then quenched by the addition of methanol (0.1 mL). Stirring was continued for 10 min at 0 °C and then saturated aqueous $NaHCO_3$ solution (5 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash chromatography on a 3 × 10 cm silica gel column, eluting with 15 % EtOAc/hexanes (500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (4-10) were combined and concentrated under reduced pressure to provide the product TBS ether **2.92** (63.5 mg, 82% over 2 steps) as a colorless oil: R_f = 0.57 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = -2.9 (*c* = 0.31, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.45 (d, *J* = 7.8 Hz, 1H), 7.30-7.20 (m, 5H), 5.87 (dd, *J* = 16.1, 7.8 Hz, 1H), 5.84 (s, 1H), 5.48 (s, 1H), 4.74 (ABq, *J* = 6.8 Hz, Δν = 6.3 Hz, 2H), 4.57 (s, 2H), 4.15-4.08 (m, 2H), 3.87 (dd, *J* = 6.4, 4.4 Hz, 1H), 3.64 (s, 3H), 3.49 (dd, *J* = 16.1, 2.0 Hz, 1H), 3.30 (s, 3H), 2.30 (dd, *J* = 14.2, 13.7 Hz, 1H), 2.13 (ddd, *J* = 16.1, 7.3, 7.3 Hz, 1H), 2.04 (ddd, *J* = 16.1, 7.3, 7.3 Hz, 1H), 1.98 (ddd, *J* = 14.2, 8.8, 2.4 Hz, 1H), 1.59 (ddd, *J* = 14.2, 8.8, 2.9 Hz, 1H), 1.51-1.44 (m, 1H), 1.25-1.15 (m, 10H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.11 (s, 3H), 1.08 (s, 3H), 0.82 (s, 9H), 0.80 (t, J = 6.8 Hz, 3H), 0.03 (s, 3H), 0.0 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 194.8, 172.1, 167.1, 166.4, 151.8, 137.9, 128.7, 128.0 (×2), 127.3, 117.9, 102.6, 93.3, 75.1, 70.8, 70.3, 69.6, 69.2, 51.9, 51.5, 47.6, 38.7, 34.6, 33.2, 31.8, 29.1 (×2), 26.1, 24.8, 23.7, 22.8, 22.1, 18.3, 14.3, 13.9, -3.8, -4.5; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 51.9, 51.5, 26.1, 23.7, 22.2, 14.3, 13.9, -3.8, -4.5; CH_2 δ 93.3, 69.6, 38.7, 34.6, 33.2, 31.8, 29.1 (×2), 24.8, 22.8; CH δ 194.8, 167.1, 128.7, 128.0 (×2), 127.3, 117.9, 75.1, 70.8, 70.3, 69.2; CH0 δ 172.1, 166.4, 151.8, 137.9, 102.6,

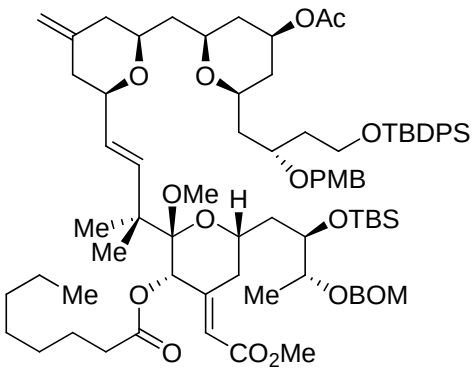
47.6, 18.3; IR (neat) 2953, 2930, 2857, 1746, 1722, 1689, 1627, 1512, 1463, 1435, 1380, 1301, 1255, 1228, 1156, 1110, 1071, 1043, 836, 776, 736, 698 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{41}H_{66}O_{10}Na$ (M+Na) 769.4323, found 769.4335.



Preparation of (2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((tert-butyl dimethylsilyl)oxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*R*,4*S*,6*S*)-6-((*S*)-4-((tert-butyldiphen ylsilyl)oxy)-2-((4-methoxybenzyl)oxy)butyl)-4-hydroxytetrahydro-2H-pyran-2-yl)me thyl)-4-methylenetetra hydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene) tetrahydro-2H-pyran-3-yl octanoate (2.108). To a stirring solution of hydroxyallylsilane **2.57** (24.2 mg, 0.0336 mmol, 1.3 equiv) and aldehyde **2.92** (19.3 mg, 0.0258 mmol, 1.0 equiv) in Et_2O (4.3 mL) in a 15 mL rb flask at -78 ºC was added a solution of TMSOTf in Et_2O (33.6 µL of 1.0 M, 0.0336 mmol, 1.3 equiv) dropwise via syringe. After 2 h at -78 ºC, the mixture was slowly warmed to -15 ºC and stirred for 1 h, and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 mL). The mixture was warmed to rt, and then the phases were separated, and the aqueous phase was extracted with Et_2O (3×10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3×11 cm silica gel

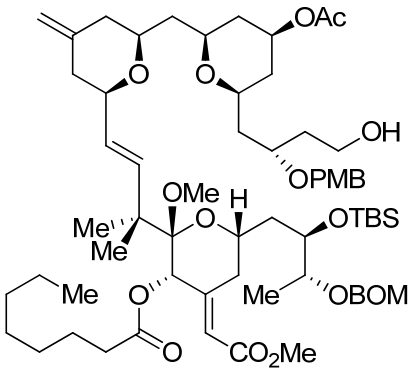
column, eluting with 40% EtOAc/hexanes, collecting 18 × 150 mm test tube fractions. The product containing fractions (4-7) were combined and concentrated under reduced pressure to give the product **2.108** (25.5 mg, 72% yield) as a colorless oil. R_f = 0.49 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = +10.1 (*c* = 0.47, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) 125 MHz ($CDCl_3$) 7.70-7.65 (m, 4H), 7.44-7.30 (m, 11H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 5.93 (d, *J* = 16.1 Hz, 1H), 5.89 (s, 1H), 5.61 (s, 1H), 5.42 (dd, *J* = 16.1, 5.9 Hz, 1H), 4.79 (s, 2H), 4.66-4.59 (m, 2H), 4.64 (s, 2H), 4.40 (ABq, *J* = 10.7 Hz, Δν = 37.6 Hz, 2H),4.12-4.06 (m, 2H), 3.93-3.89 (m, 1H), 3.88 -3.72 (m, 5H), 3.80 (s, 3H), 3.68 (s, 3H), 3.60-3.47 (m, 4H), 3.31 (s, 3H), 2.40-2.28 (m, 3H), 2.24 (d, *J* = 13.2 Hz, 1H), 2.16 (d, *J* = 13.7 Hz, 1H), 2.02-1.85 (m, 6H), 1.84 -1.73 (m, 3H), 1.67-1.50 (m, 6H), 1.32-1.22 (m, 10H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.12 (s, 3H), 1.11 (s, 3H), 1.04 (s, 9H), 0.90-0.85 (m, 3H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); 13C NMR ($CDCl_3$) δ 172.3, 166.6, 159.3, 153,3, 144.4, 138.0, 137.9, 135.8, 134.1, 134.0, 131.2, 129.8, 129.5 (×2), 128.6, 128.0, 127.8, 127.6, 116.6, 114.0, 109.0, 102.6, 93.2, 79.2, 75.0 (×2), 72.7, 72.0 (x3), 71.5, 70.2, 69.5, 68.4 (×2), 60.6, 55.5, 51.5, 51.3, 46.2, 42.5, 42.4, 41.8, 41.3, 41.0, 40.5, 38.7, 37.9, 34.6, 33.8, 31.9, 29.3, 29.2, 27.2, 26.1, 25.0, 24.4, 24.0, 22.8, 19.4, 18.3, 14.3, 14.0, -3.8, -4.4; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 51.5, 51.3, 27.2, 26.1, 24.4, 24.0, 14.3, 14.0, -3.8, -4.4; CH_2 δ 109.0, 93.2, 72.0, 69.5, 60.6, 42.5, 42.4, 41.8, 41,3, 41.0, 40.5, 38.7, 37.9, 34.6, 33.8, 31.9, 29.3, 29.2, 25.0, 22.8; CH δ 137.9, 135.8, 129.8, 129.5 (×2), 128.6, 128.0, 127.8, 127.6, 116.6, 114.0, 79.2, 75.0, 72.7, 72.0 (×2), 71.5, 70.2, 68.4 (×2); CH_0 δ 172.3, 166.6, 159.3, 153.3, 144.3, 138.0, 134.1, 134.0, 131.2, 102.6, 46.2, 19.4, 18.3; IR (neat) 3473, 3069, 2932, 2856, 1743, 1720, 1653, 1611, 1512, 1464, 1430, 1380,

1360, 1248, 1155, 1107, 1041, 890, 834, 737, 613 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{80}H_{118}O_{15}Si_2Na$ (M+Na) 1397.7907, found 1397.7913.



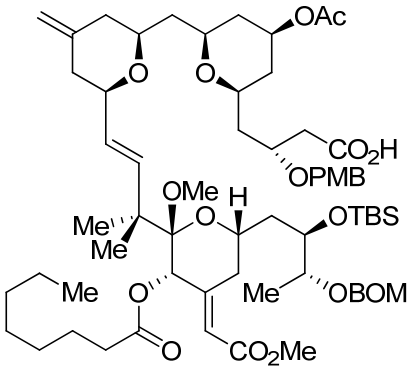
Preparation of (2*S*,3*S*,6*S*,*E*)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*S*,4*S*,6*R*)-4-acetoxy-6-((*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-2-((4-methoxybenzyl)oxy)butyl)tetrahydro-2H-pyran-2-yl)methyl)-4-methylenetetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((*tert*-butyldimethylsilyl)oxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2H-pyran-3-yl octanoate (2.91). To a stirring solution of the alcohol **2.108** in CH_2Cl_2 (14 mL, 0.003 M) in a 25 mL rb flask at rt were added pyridine (168 mg, 2.13 mmol, 50 equiv), 4-dimethylaminopyridine (51.9 mg, 0.425 mmol, 10 equiv) and Ac_2O (130 mg, 1.28 mmol, 30 equiv). The mixture was stirred at rt overnight, and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash chromatography with a 3 × 18 cm silica gel column, eluting with 40% EtOAc/hexanes, collecting 18 × 150 mm test tube fractions. The product containing fractions (4-6) were combined and concentrated under reduced pressure to provide the product **2.91** (60.8 mg, quant. yield)

as a colorless oil: R_f = 0.40 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +15 (c = 0.17, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) 125 MHz ($CDCl_3$) 7.70-7.65 (m, 4H), 7.45-7.32 (m, 11H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.93 (d, *J* = 16.1 Hz, 1H), 5.89 (s, 1H), 5.58 (s, 1H), 5.42 (dd, *J* = 16.1, 5.4 Hz, 1H), 4.80 (s, 2H), 4.65-4.59 (m, 3H), 4.53 (bs, 1H), 4.44 (d, *J* = 10.7 Hz, 1H), 4.34 (d, *J* = 10.7 Hz, 1H), 4.11-4.05 (m, 2H), 3.91-3.82 9m, 2H), 3.80 (s, 3H), 3.79-3.72 (m, 2h), 3.68 (s, 3H), 3.67-3.60 (m, 2H), 3.58-3.45 (m, 3H), 3.30 (s, 3H), 2.38-2.30 (m, 3H), 2.26 (d, *J* = 12.7 Hz, 1H), 2.17 (d, *J* = 14.7 Hz, 1H), 2.04 (s, 3H), 2.06-1.95 (m, 3H), 1.92-1.85 (m, 2H), 1.81-1.73 (m, 3H), 1.66-1.54 (m, 6H), 1.33-1.23 (m, 10H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.11 (s, 6H), 1.05 (s, 9H), 0.90-0.85 (m, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); 13C NMR ($CDCl_3$) δ 172.4, 170.6, 166.7, 159.4, 153,1, 144.2, 138.1, 138.1, 135.8, 134.1, 134.0, 131.2, 129.8, 129.5, 128.6, 128.0, 127.9, 127.3, 117.0, 114.1, 109.1, 102.6, 93.3, 79.0, 75.0, 74.9, 72.8, 72.0, 71.8, 71., 70.7, 70.3, 69.5, 68.4, 60.6, 55.5, 51.6, 51.3, 46.1, 42.8, 42.3, 40.8, 40.4, 38.7, 37.9 (×2), 37.8, 34.6, 33.5, 31.9, 29.3, 29.2, 27.1, 26.1, 24.9, 24.2, 24.1, 22.8, 21.5, 19.4, 18.3, 14.0, -3.9, -4.4; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 51.6, 51.3, 27.1, 26.1, 24.4, 24.1, 21.5, 14.3, 14.0, -3.9, -4.4; CH_2 δ 109.1, 93.3, 72.2, 69.5, 60.6, 42.8, 42.3, 40.8, 40,4, 38.7, 37.9 (×2), 37.8, 34.6, 33.5, 31.9, 29.3, 29.2, 24.9, 22.8; CH δ 138.1, 135.8, 131.1, 129.8, 129.5, 128.6, 128.0, 127.9, 127.3, 117.0, 114.1, 79.0, 75.0, 74.9, 72.8, 72.0, 71.8, 71.5, 70.7, 70.3, 68.4; CH0 δ 172.4, 170.6, 166.7, 159.4, 153.1, 144.2, 128.1, 134.1, 134.0, 102.6, 46.1, 19.4, 18.3; IR (neat) 2952, 2856, 2811, 1741, 1722, 1652, 1611, 1513, 1462, 1428, 1379, 1361, 1246, 1160, 1110, 1083, 1041, 972, 835, 775, 737, 701 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{82}H_{120}O_{16}Si_2Na$ (M+Na) 1439.8013, found 1439.8004.



Preparation of (2*S*,3*S*,6*S*,*E*)-2-((*E*)-4-((2*R*,6*S*)-6-(((2*S*,4*S*,6*R*)-4-acetoxy-6-((*S*)-4-hydroxy-2-((4-methoxybenzyl)oxy)butyl)tetrahydro-2H-pyran-2-yl)methyl)-4-methylene tetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((*tert*-butyldimethylsilyl)oxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2H-pyran-3-yl octanoate (2.109). To a stirring solution of TBDPS silyl ether **2.91** (30.0 mg, 0.0212 mmol, 1.0 equiv) in DMF (2.1 mL, 0.01 M) in a 15 mL rb flask, were added a solution of TBAF solution in THF (42.3 μL of 1.0 M, 0.0423 mmol, 2.0 equiv) and a solution of AcOH solution in DMF (42.3 μL of 1.0 M, 0.0423 mmol, 2.0 equiv). The solution was stirred at rt for 2 days, and then diluted with 40% EtOAc/hexanes (100 mL) and water (5 mL). The phases were separated and the organic phase was washed with water (3 × 10 mL). The organic phases were dried over Na_2SO_4, filtered, and then concentrated under reduced pressure. Purification was accomplished using flash chromatography on a 2 × 15 cm silica gel column, eluting with 30% EtOAc/hexanes (500 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (26-41) were combined and concentrated under reduced pressure to provide the alcohol **2.109** (21.4 mg, 86%) as a colorless oil. R_f = 0.33(30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +19 (*c* = 0.20, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) 125 MHz ($CDCl_3$) 7.36-7.28 (m, 5H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.94 (dd, *J*

= 16.1, 1.0 Hz, 1H), 5.89 (s, 1H), 5.57 (s, 1H), 5.43 (dd, *J* = 16.1, 5.9 Hz, 1H), 4.95-4.88 (m, 1H), 4.80 (s, 2H), 4.68-4.57 (m, 2H), 4.64 (s, 2H), 4.47 (ABq, *J* = 10.7 Hz, , Δν = 33.5 Hz, 2H), 4.12-4.05 (m, 3H), 3.90-3.83 (m, 3H), 3.81 (s, 3H), 3.76-3.70 (m, 2H), 3.69 (s, 3H), 3.62-3.45 (m, 4H), 3.30 (s, 3H), 2.39-2.30 (m, 1H), 2.34 (td, *J* = 7.3, 2.4 Hz, 2H), 2.25 (d, *J* = 13.2 Hz, 1H), 2.18 (d, *J* = 12.7 Hz, 1H), 2.04 (s, 3H), 2.04-1.88 (, 7H), 1.80-1.70 (m, 2H), 1.70-1.52 (m, 6H), 1.33-1.23 (m, 10H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.10 (s, 6H), 0.90-0.85 (m, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.4, 170.7, 166.7, 159.6, 153.1, 144.2, 138.4, 138.1, 130.5, 129.7, 128.6, 128.0, 127.9, 127.2, 117.0, 114.2, 109.1, 102.6, 93.2, 79.3, 75.2, 75.0 (×2), 72.4, 72.2, 72.0, 71.5, 70.5, 70.2, 69.5, 68.4, 60.3, 55.5, 51.6, 51.3, 46.1, 42.7, 41.6, 40.8, 40.3, 38.6, 38.0, 37.6, 36.8, 34.6, 33.5, 31.9, 29.3, 29.2, 26.1, 24.9, 24.2, 24.1, 22.8, 21.5, 18.3, 14.3, 14.0, -3.8, -4.5; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 51.6, 51.3, 26.1, 24.2, 24.1, 21.5, 14.3, 14.0, -3.8, -4.5; CH_2 δ 109.1, 93.2, 72.2, 69.5, 60.3, 42.7, 41.6, 40.8, 40.3, 38.6, 38.0, 37.6, 36.8, 34.6, 33.5, 31.9, 29.3, 29.2, 24.9, 22.8; CH δ 138.4, 129.7, 128.6, 128.0, 127.9, 127.2, 117.0, 114.2, 79.3, 75.2, 75.0 (×2), 72.4, 72.0, 71.5, 70.5, 70.2, 68.4; CH_0 δ 172.4, 170.7, 166.7, 159.6, 153.1, 144.2, 138.1, 130.5, 102.6, 46.1, 18.3; IR (neat) 3493, 2951, 2930, 2891, 2856, 1740, 1723, 1612, 1513, 1462, 1434, 1378, 1361, 1301, 1245, 1160, 1108, 1040, 895, 775, 737, 697, 667 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{66}H_{102}O_{16}SiNa$ (M+Na) 1201.6835, found 1201.6843.

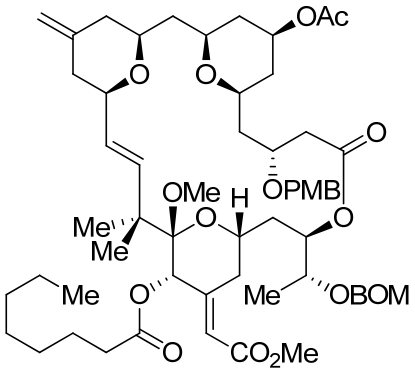


Preparation of (*R*)-4-((2*R*,4*S*,6*S*)-4-acetoxy-6-(((2*S*,6*R*)-6-((*E*)-3-((2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((*tert*-butyldimethylsilyl)oxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-3-(octanoyloxy)tetrahydro-2H-pyran-2-yl)-3-methylbut-1-en-1-yl)-4-methylenetetrahydro-2H-pyran-2-yl)methyl)tetrahydro-2H-pyran-2-yl)-3-((4-methoxybenzyl)oxy)butanoic acid (2.110). To a stirring solution of alcohol **2.109** (37.2 mg, 0.0315 mmol, 1.0 equiv) in CH_2Cl_2 (3.2 mL, 0.01M) in a 25 mL rb flask at 0 °C were added diisopropylethylamine (85.6 mg, 0.662 mmol, 21.0 equiv) and then dimethyl sulfoxide (73.8 mg, 0.947 mmol, 30.0 equiv). The solution was stirred at 0 °C for 5 min and $SO_3 \cdot Py$ (30.1 mg, 0.189 mmol, 6.0 equiv) was added in one portion. Stirring was continued at 0 °C for 1.25 h, after which the reaction mixture was diluted with CH_2Cl_2 (1 mL) and quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL). The mixture was stirred at rt for 10 min until effervescence was complete. The reaction mixture was partitioned between CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×25 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was washed through a small plug of silica gel with 20 % EtOAc/hexanes (100 mL), and the

solvent was removed under reduced pressure to provide the aldehyde, which was used in the next step without further purification.

To a stirring solution of the aforementioned aldehyde in 2-methyl-2-butene (3.5 mL) and *tert*-butyl alcohol (3.5 mL) in a 25 rb flask at rt was added aqueous solution of KH_2PO_4 (670 μL of 1.25 M). The mixture was cooled to 0 °C, and $NaClO_2$ (80%, 71.2 mg, 0.630 mmol, 20.0 equiv) was added in one portion. The reaction mixture was stirred vigorously at 0 °C for 4 h, and then quenched by the addition of aqueous pH 4 buffer solution (5 mL). The resulting mixture was partitioned between CH_2Cl_2 (25 mL) and aqueous pH 4 buffer solution (5 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. Purification was accomplished using flash chromatography with a 3 × 13 cm silica gel column, eluting with 5 % methanol/30 % EtOAc/hexanes, collecting 18 × 150 mm test tube fractions. The product containing fractions (6-10) were combined and concentrated under reduced pressure to provide the product carboxylic acid **2.110** (37.5 mg, quant. yield over 2 steps) as a colorless oil: R_f = 0.12 (5% methanol/30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +20 (*c* = 0.19, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) 7.37-7.28 (m, 5H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.95 (d, *J* = 16.1 Hz, 1H), 5.90 (s, 1H), 5.58 (s, 1H), 5.42 (dd, *J* = 15.6, 6.3 Hz, 1H), 4.94-4.87 (m, 1H), 4.81 (ABq, *J* = 6.8 Hz, Δν = 4.5 Hz, 2H), 4.65 (ABq, *J* = 11.7 Hz, Δν = 5.2 Hz, 2H), 4.64-4.58 (m, 2H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.43 (d, *J* = 10.7 Hz, 1H), 4.14-4.05 (m, 3H), 3.88-3.83 (m, 1H), 3.80 (s, 3H), 3.80-3.70 (m, 2H), 3.69 (s, 3H), 3.63-3.44 (m, 4H), 3.31 (s, 3H), 2.61 (d, *J* = 5.9 Hz, 2H), 2.40-2.30 (m, 2H), 2.25 (d, *J* = 12.7 Hz, 1H), 2.17 (d, *J* = 13.2 Hz, 1H), 2.07-1.90 (m, 7H), 2.03 (s, 3H), 1.77-1.55 (m, 7H), 1.34-1.24

(m, 10H), 1.16 (d, J = 6.4 Hz, 3H), 1.11 (s, 6H), 0.90-0.85 (m, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 174.5, 172.5, 170.7, 166.7, 159.6, 153.2, 144.1, 138.7, 138.0, 130.3, 129.7, 128.6, 128.1, 127.9, 127.2, 116.9, 114.1, 109.2, 102.6, 93.1, 79.4, 75.2, 75.1, 75.0, 73.0, 72.4, 72.0, 71.6, 70.4, 70.1, 69.5, 68.4, 55.5, 51.6, 51.4, 46.1, 42.7, 41.9, 40.8, 40.4, 40.1, 38.6, 37.8, 37., 34.6, 33.5, 31.9, 29.2 (×2), 26.1, 24.9, 24.3, 24.0, 22.8, 21.5, 18.3, 14.3, 14.0, -3.8, -4.5; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 51.6, 51.4, 26.1, 24.3, 24.0, 21.5, 14.3, 14.0, -3.8, -4.5; CH_2 δ 109.2, 93.1, 72.4, 69.5, 42.7, 41.9, 40.8, 40.4, 40.1, 38.6, 37.8, 37.6, 34.6, 33.5, 31.9, 29.2 (×2), 24.9, 22.8; CH δ 138.7, 129.7, 128.6, 128.1, 127.9, 127.2, 116.9, 114.1, 79.4, 75.2, 75.1, 75.0, 73.0, 72.0, 71.6, 70.4, 70.1, 68.4; CH_0 δ 174.5, 172.5, 170.7, 166.7, 159.6, 153.2, 144.1, 138.0, 130.3, 102.6, 46.1, 18.3; IR (neat) 2951, 2931, 2885, 2857, 1738, 1724, 1681, 1651, 1613, 1548, 1463, 1434, 1380, 1245, 1161, 1108, 1073, 1040, 97-, 913, 835, 776, 746, 698 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{66}H_{100}O_{17}SiNa$ (M+Na) 1215.6628, found 1215.6644.

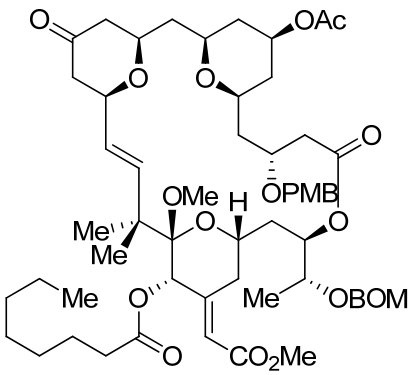


Preparation of Protected (1*S*,3*S*,7*R*,8*E*,11*S*, 12*S*,13*E*,15*S*,17*R*,21*R*,23*R*,25*S*)-25-acetoxy-17-((*R*)-1-((benzyloxy)methoxy)ethyl)-11-methoxy-13-(2-methoxy-2-oxoethylidene)-21-((4-methoxybenzyl)oxy)-10,10-dimethyl-5-methylene-19-oxo-18,27,28

,29-tetraoxatetra cyclo [21.3.1.13,7 .111,15]nonacos-8-en-12-yl octanoate (2.75). To a stirring solution of TBS ether **2.110** (12.0 mg, 0.0101 mmol, 1.0 equiv) in 9:1 THF/pyridine (1.0 mL, 0.01 M) in a 4 mL plastic vial were added methanol (0.1 mL) and HF·Py (20 %, 0.41 mL). The solution was stirred at rt for 48 h, and then diluted with 50 % EtOAc/hexanes (100 mL), and washed with brine (2 × 10 mL). The solution was dried over Na_2SO_4 and concentrated under reduced pressure. The crude seco acid was taken on to the next step without purification.

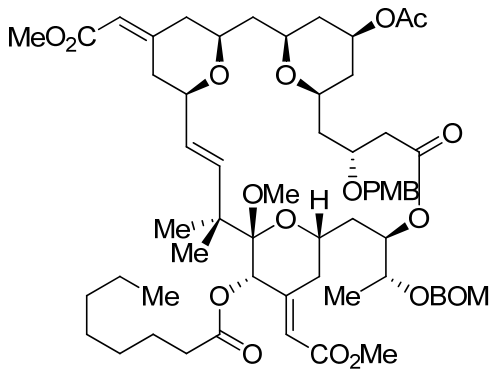
To a stirring solution of aforementioned seco acid in THF (0.34 mL) in a 4 mL reaction vial at 0 °C were added triethylamine (6.1 mg, 0.0606 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoyl chloride (7.4 mg, 0.303 mmol, 3.0 equiv). After 5 min the mixture was warmed to rt and stirring was continued for an additional 3 h. The reaction mixture was diluted with 3:1 toluene/THF (4.0 mL, 0.0025 M) and placed into a 25 mL gas-tight syringe. This solution was added by syringe pump to a stirring solution of 4-dimethylaminopyridine (24.7 mg, 0.202 mmol, 20.0 equiv) in toluene (6.7 mL, 0.0015 M) that was maintained at 40 °C over 12 h. The residual contents of the syringe were rinsed into the flask with toluene (2 × 1.0 mL) and stirring was continued for an additional 2 h. The reaction mixture was then cooled to rt, diluted with 40% EtOAc/hexanes (100 mL), and washed with water (3 × 10 mL) and with brine (10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash chromatography with a 2 × 12 cm silica gel column, eluting with 30% EtOAc/hexanes, collecting 13 × 100 mm test tube fractions. The product containing fractions (4-7) were combined and concentrated under

reduced pressure to provide pure macrolactone **2.111** (7.3 mg, 61% over 2 steps) as a colorless oil.



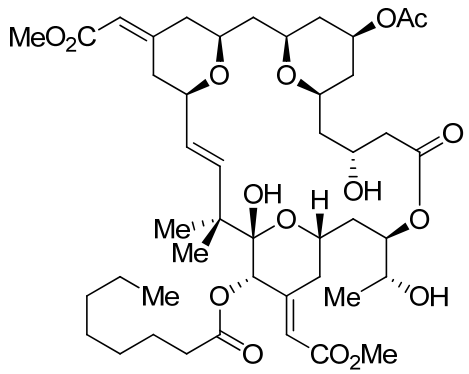
Pr**eparation of ketone (1*S*,3*R*,7*R*,8*E*,11*S*,12*S*,13*E*,15*S*,17*R*,21*R*,23*R*,25*S*)-25-acetoxy-17-((*R*)-1-((benzyloxy)methoxy)ethyl)-11-methoxy-13-(2-methoxy-2-oxoethylidene)-21-((4-methoxybenzyl)oxy)-10,10-dimethyl-5,19-dioxo-18,27,28,29-tetraoxatetracyclo [21.3.1.13, 7.111,15] nonacos-8-en-12-yl octanoate (2.111).** A 100 ml flask containing 50 mL of CH_2Cl_2 was cooled to -78 °C, and a stream of O_3 was passed in for 3 min. The color of the solution changed to light blue. The flask was sealed and kept at -78 °C for immediate use. This O_3 solution was added in 50 μL portion via a plastic syringe to a stirring solution of olefin **2.75** (1.8 mg, 0.0017 mmol, 1.0 equiv) at -78 °C. The reaction was monitored by TLC and the addition of the O_3 solution was continued every 10 min until the starting material was fully consumed. Dimethyl sulfide (0.1 mL) was then added and the mixture was warmed to rt. The solution was stirred at rt for 12 h after which the solvent was removed under reduced pressure. Purification was accomplished using flash chromatography on a 1 × 8 cm silica gel column, eluting with 40% EtOAc/hexanes (250 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (11-16) were combined and concentrated under reduced pressure to

provide ketone **2.111** (1.4 mg, 78%) as a colorless oil. R_f = 0.49 (40% EtOAc/hexanes); $[\alpha]_D^{20}$ = +32 (*c* = 0.05, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.38-7.28 (m,5H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.27 (d, *J* = 15.6 Hz, 1H), 5.94 (d, *J* = 1.5 Hz, 1H), 5.59-5.53 (m, 1H), 5.33 (dd, *J* = 15.6, 8.8 Hz, 1H), 5.18 (s, 1H), 4.80 (s, 2H), 4.62 (ABq, *J* = 11.7, , Δν = 14.4 Hz, 2H), 4.42 (ABq, *J* = 11.2 Hz, , Δν = 7.0 Hz, 2H), 42.9-4.22 (m, 1H), 4.16-4.10 (m, 1H), 3.90 (dd, *J* = 6.4, 4.4 Hz, 1H), 3.77-3.74 (m, 1H), 3.76 (s, 3H), 3.70-3.65 (m, 3H), 3.67 (s, 3H), 3.48-3.40 (m, 1H), 3.14-3.08 (m, 1H), 3.06 (s, 3H), 2.50-2.40 (m, 2H), 2.35-2.18 (m, 4H), 2.16-2.06 (m, 2H), 2.02 (s, 3H), 1.96-1.76 (m, 5H), 1.64-1.50 (m, 6H), 1.34-1.22 (m, 10H), 1.10-1.06 (m, 9H), 0.86 (t, *J* = 6.3 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 206.8, 172.3, 172.2, 170.7, 167.0, 159.5, 151.3, 142.7, 138.1, 130.6, 129.8, 128.7, 128.0, 127.9, 124.3, 119.6, 114.0, 103.3, 93.7, 79.8, 77.4, 74.5, 74.4, 73.6, 73.4, 72.7, 71.8, 70.9, 70.2, 69.9, 67.3, 55.5, 52.7, 51.4, 48.9, 48.2, 45.3, 43.9, 42.9, 41.4, 37.6, 35.0, 34.8, 31.8, 31.0, 29.2 (×2), 29.1, 26.4, 24.9, 22.8, 21.5, 20.1, 15.4, 14.3; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 52.7, 51.4, 26.4, 21.5, 20.1, 15.4, 14.3; CH_2 δ 93.7, 71.8, 69.9, 48.9, 48.2, 43.9, 42.9, 41.4, 37.6, 35.0, 34.8, 31.8, 31.0, 29.2 (×2), 29.1, 24.9, 22.8; CH δ 142.7, 129.8, 128.7, 128.0, 127.9, 124.3, 119.6, 114.0, 79.8, 77.4, 74.5, 74.4, 73.6, 73.4, 72.7, 70.9, 70.2, 67.3; CH_0 δ 206.8, 172.3, 172.2, 170.7, 167.0, 159.5, 151.3, 138.1, 130.6, 103.3, 45.3; IR (neat) 2934, 2857, 2347, 1732, 1652, 1540, 1457, 1363, 1150, 1119, 1038, 747, 703 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{59}H_{82}O_{17}Na$ (M+Na) 1085.5450, found 1085.5442.



Preparation of (2*Z*,2'*E*)-dimethyl 2,2'-((1*S*,3*S*,7*R*,11*S*,12*S*,15*S*,17*R*,21*R*, 23*R*, 25*S*,*E*)-25-acetoxy-17-((*R*)-1-((benzyloxy)vmethoxy)ethyl)-11-methoxy-21-((4-metho xybenzyl)oxy)-10,10-dimethyl-12-(octanoyloxy)-19-oxo-18,27,28,29-tetraoxatetracycl o[21.3.1.13,7.111,15]nonacos-8-ene-5,13-diylidene)diacetate (2.113). A stirring solution of chiral *R*-BINOL phosphonoacetate **2.112** (26.3 mg, 0.65 mmol, 50 equiv) in THF (0.65 mL, 0.002 M) was cooled in an ice water bath under N_2. A solution of KHMDS in THF (0.039 mL of 1.0 M, 0.039 mmol, 30 equiv) was then added dropwise. After 15 min, the resulting cloudy white mixture was added to neat ketone **2.111** (1.4 mg, 0.0013 mmol, 1.0 equiv) in a reaction vial, previously cooled in an ice water bath. The resulting mixture was stirred overnight at 0 °C. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl (1.0 mL). The biphasic mixture was diluted with water (5 mL) and Et_2O (10 mL). The aqueous phase was separated and extracted with Et_2O (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using flash chromatography on a 1 × 8 cm silica gel column, eluting with 35% EtOAc/hexanes (100 mL), collecting 12 × 75 mm test tube fractions. The product containing fractions (4-8) were combined and concentrated under reduced pressure to provide a mixture of *Z*:*E* (4:1) enoate **2.113** (1.2 mg, 82% yield) as a colorless oil. The The *E* and *Z* diastereomers

were further separated using preparative thin layer chromatography eluting with 10% acetone/benzene providing 0.8 mg of the desired *Z* isomer as a colorless oil. R_f = 0.45 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = +48 (c = 0.07, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.30 (m, 5H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 6.23 (d, *J* = 15.6 Hz, 1H), 5.95 (d, *J* = 2.0 Hz, 1H), 5.74 (s, 1H), 5.55 (ddd, *J* = 11.9, 4.3, 2.4 Hz, 1H), 5.35 (dd, *J* = 15.6, 8.3 Hz, 1H), 5.18 (s, 1H), 4.85-4.80 (m, 4H), 4.64 (s, 2H), 4.46 (ABq, *J* = 10.7Hz, , Δν = 8.5 Hz, 2H), 4.17-4.13 (m, 1H), 4.00-3.90 (m, 2H), 3.76-3.74 (m, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H), 3.59-3.54 (m, 1H), 3.50-3.44 (m, 1H), 3.20-3.14 (m, 1H), 3.07 (s, 3H), 2.54-2.44 (m, 2H), 2.31-2.25 (m, 3H), 2.12-1.98 (m, 2H), 2.03 (s, 3H), 1.94-1.84 (m, 4H), 1.84-1.72 (m, 3H), 1.65-1.50 (m, 5H), 1.32-1.22 (m, 10H), 1.11-1.05 (m, 9H), 0.87 (t, *J* = 6.7 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.3 (×2), 170.8, 167.1, 167.0, 159.4, 157.3, 151.5, 142.3, 138.1, 130.8, 129.6, 128.6, 128.1, 127.9, 125.4, 119.5, 114.9, 113.9, 103.4, 93.8, 80.5, 77.4, 75.6, 75.0, 73.7, 73.4 (×2), 72.0, 70.9, 70.3, 69.8, 67.3, 55.5, 52.8, 51.4, 51.2, 45.3, 44.0, 43.6, 42.9, 41.3, 37.6, 36.1, 34.9, 34.8, 31.9, 31.0, 29.9, 29.2, 29.1, 26.4, 24.9, 22.8, 21.5, 20.2, 15.4, 14.3; 125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 55.5, 52.8, 51.4, 51.2, 26.4, 21.5, 20.2, 15.4, 14.3; CH_2 δ 93.8, 72.0, 69.8, 44.0, 43.6, 42.9, 41.3, 37.6, 36.1, 34.9, 34.8, 31.9, 31.0, 29.9, 29.2, 29.1, 24.9, 22.8; CH δ 142.3, 129.6, 128.6, 128.1, 127.9, 125.4, 119.5, 114.9, 113.9, 80.5, 77.4, 75.6, 75.0, 73.7, 73.4 (×2), 70.9, 70.3, 67.3; CH0 δ 172.3 (×2), 170.8, 167.1, 167.0, 159.4, 157.3, 151.5, 138.1, 130.8, 103.4, 45.3; IR (neat) 2993, 1738, 1681, 1513, 1452, 1383, 1364, 1237, 1111, 1079, 1040, 821, 737, 701, 665 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{62}H_{86}O_{18}Na$ (M+Na) 1141.5712, found 1141.5707.



Preparation of (2*Z*,2'*E*)-dimethyl 2,2'-((1*S*,3*S*,7*R*,11*S*,12*S*,15*S*,17*R*, 21*R*,23*R*, 25*S*,*E*)-25-acetoxy-11,21-dihydroxy-17-((*R*)-1-hydroxyethyl)-10,10-dimethyl-12-(oct anoyloxy)-19-oxo-18,27,28,29-tetraoxatetracyclo [21.3.1.13,7.111,15] nonacos-8-ene-5,13-diylidene) diacetate (Merle 33). To a stirring solution of **2.113** (2.0 mg, 0.0018 mmol, 1.0 equiv) in CH_2Cl_2 (1.0 mL, 0.0018 M) in a 4 mL reaction vial at 0 ºC were added aqueous *tert*-butyl alcohol (0.05 mL), pH 7 buffer (0.5 mL) and DDQ (1.6 mg, 0.0072 mmol, 4.0 equiv). The reaction mixture was stirred at 0 ºC for 5 h, then diluted with CH_2Cl_2 (1 mL) and quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL). After stirring vigorously for 10 min at rt the mixture was partitioned between CH_2Cl_2 (5 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was taken on to the next step without purification.

To a 4 mL reaction vial containing the aforementioned analogue precursor was added a 0.25 M solution of $LiBF_4$ in 25:1 CH_3CN/H_2O (324 μL, 0.081 mmol, 45.0 equiv). The reaction vial was sealed and the mixture was stirred at 80 ºC for 10 h. After cooling to rt, the mixture was diluted with EtOAc (1 mL) and was quenched by addition of saturated aqueous $NaHCO_3$ solution (0.5 mL). The mixture was partitioned between

EtOAc (10 mL) and saturated aqueous $NaHCO_3$ solution (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished using flash chromatography with a 0.6 × 6 cm silica gel column, eluting with 40% EtOAc/hexanes, collecting 6 × 50 mm test tube fractions. The product containing fractions (17-31) were combined and concentrated under reduced pressure to provide analogue Merle 33 (1.1 mg, 71% over 2 steps) as a colorless oil: R_f = 0.32 (50 % EtOAc/hexanes); $[\alpha]_D^{20}$ = + 15 (*c* = 0.04, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 5.99 (d, *J* = 1.5 hz, 1H), 5.81 (d, *J* = 15.6 Hz, 1H), 5.68 (s, 1H), 5.34 (dd, *J* = 15.6 , 8.8 Hz, 1H), 5.20 (s, 1H), 5.14 (s, 1H), 4.88-4.80 (m, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.24-4.16 (m, 1H), 4.10-4.00 (m, 2H), 3.84-3.79 (m, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.67-3.63 (m, 1H), 3.63-3.57 (m, 1H), 3.52 (t, *J* = 10.7 Hz, 1H), 2.51 (dd, *J* = 10.2, 2.0 Hz, 1H), 2.42 (dd, *J* = 12.2, 11.7 Hz, 1H), 2.32 (td, *J* = 7.3, 2.4 Hz, 1H), 2.24-2.15 (m, 1H), 2.13-2.08 (m, 2H), 2.04 (s, 3H), 2.04-2.00 (m, 1H), 1.96-1.82 (m, 7H), 1.66-1.50 (m, 6H), 1.36-1.20 (m, 10H), 1.24 (d, *J* = 6.4 Hz, 3H), 1.15 (s, 3H), 1.11 (s, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 172.1 (×2), 170.7, 170.6, 167.2, 156.7, 152.1, 139.6, 129.4, 119.8, 114.6, 99.1, 79.3, 77.2, 76.7, 74.4, 73.9, 73.6, 70.5, 69.5, 68.7, 64.7, 51.2 (×2), 45.2, 43.9, 43.1, 42.7, 39.9, 37.4, 36.7, 36.1, 34.9, 31.9, 31.5, 29.9, 29.3, 29.1, 24.9, 22.9, 22.8, 21.5,20.1, 20.0, 14.3;v125 MHz DEPT NMR ($CDCl_3$) CH_3 δ 51.2 (×2), 29.1, 21,5 20.1, 20.0, 14.3; CH_2 δ 43.9, 43.1, 42.7, 39.9, 37.4, 36.7, 36.1, 34.9, 31.9, 31.5, 29.9, 29.3, 24.9, 22.9, 22.8; CH δ 139.6, 129.4, 119.8, 114.6, 79.3, 77.2, 76.7, 74.4, 73.9, 73.6, 70.5, 69.5, 68.7, 64.7; CH0 δ 172.1 (×2), 170.7, 170.6, 167.2, 156.7,

152.1, 99.1, 45.2; IR (neat) 2930, 2360, 2342, 1733, 1470, 1426, 1263, 1245, 1166, 1110, 1037 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{45}H_{68}O_{16}Na$ (M+Na) 887.4405, found 887.4423.

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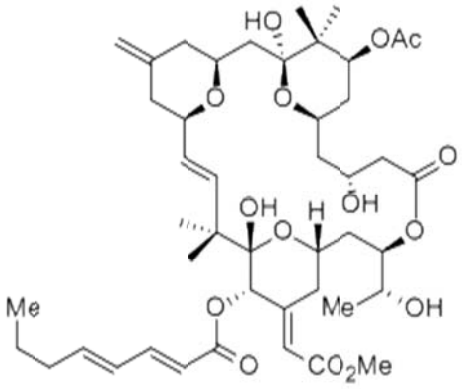
CHAPTER 3

SYNTHETIC STUDY OF A BRYOSTATIN ANALOGUE WITH A C9 HEMIKETAL

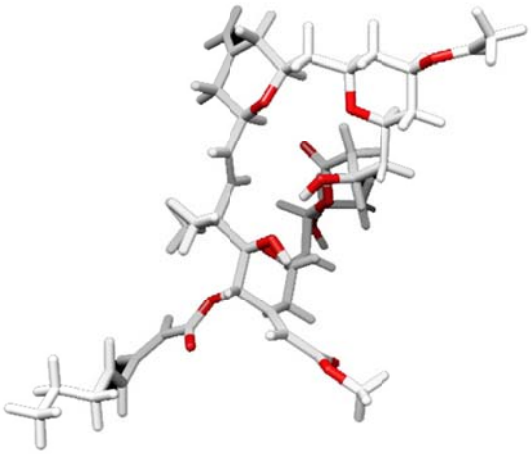
Introduction

Our group has been interested in addressing the supply of bryostatin through the synthesis of bryostatin analogues. All the results from the biological tests on our bryostatin analogues suggest the northern hemisphere of bryostatin 1 plays a critical role responsible for its unique biological activities as antagonist to phorbol ester. Our focus of bryostatin analogue study has evolved from just the preparation of bryostatin analogues with similar or higher binding affinity with PKC in comparison with bryostatin 1 to identifying the pharmacophoric groups responsible for the unique bioactivities of bryostatin 1.

Our next interesting site is the C9 hydroxyl group. In cooperation with Dr. Peach in NIH, we were able to perform the molecular docking studying of analogues on the C1 domain of PKCδ (Figure 3.1).[1] The docking results indicated (1) the conformational search of Merle 28 itself in water and octanol solvents has a single well-defined low-energy conformer, due to the intramolecular hydrogen bonding between the hydroxyl groups at C3 and C19; (2) the docking of Merle 28 into the C1 domain binding site is straightforward, because there is essentially no major conformational change between the



Merle 28



Computational structure of Merle 28

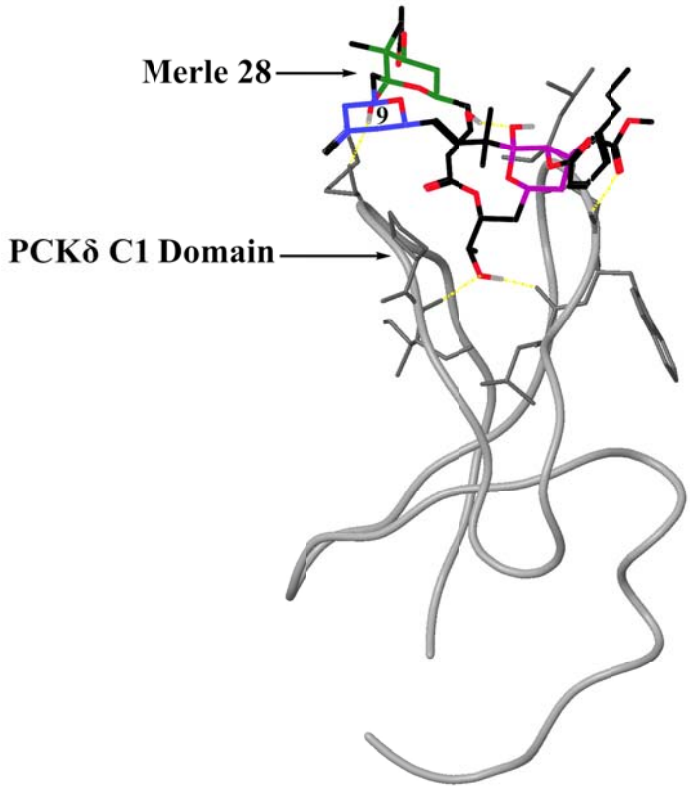


Figure 3.1 The docking results of Merle 28 to the C1 Domain of PKCδ

crystal, solvent and bound states, which is also supported by the results from the X-ray structure of PKCδ C1-PMA complex; (3) In this binding mode, the A and B rings lie above the binding site in the plane of the bilayer. The only direct interaction they make with the C1 domain is via a hydrogen bond between the hydroxyl at C9 and the backbone carbonyl oxygen of Met 259 in the C1 domain. This results is very similar to previous results reported by the Itai group with a different docking program.[2]

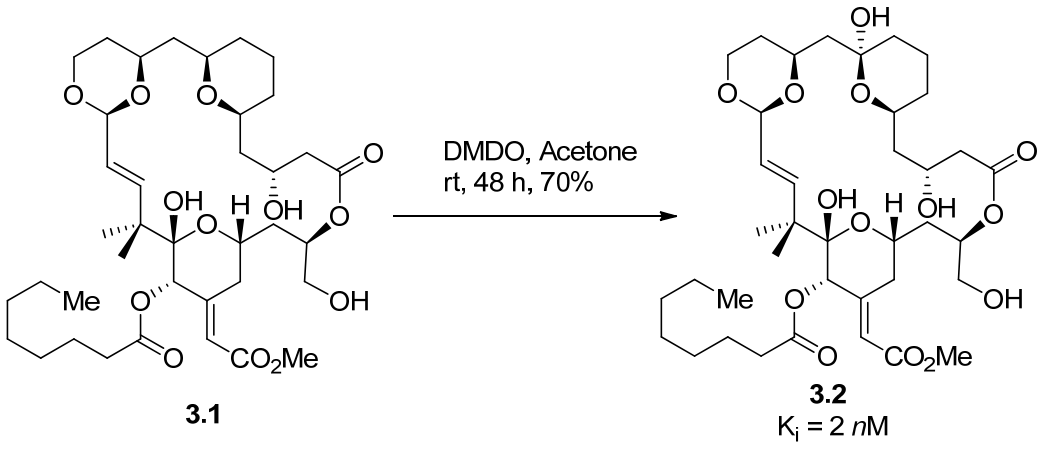
The biological results from Merle 30 indicate that the removal of C9 OH did not switch biological activities of analogue from bryostatin-like to PMA-like. We also notice that Merle 30 does show certain shift of biological activities towards PMA in both U937 and LNCaP cell lines. The importance of investigating the effect of C9 OH on the biological activities of bryostatin 1 encourages us to pursue the synthesis of bryostatin analogue with the C9 hemi-ketal functionality. The aims were (1) discovery of a convergent and efficient route to access bryostatin analogues containing the C9 hemi-ketal; (2) study of biological activities of those analogues to evaluate the effect of C9 hydroxyl group alone and with other substituents present on their biological activities.

There is limited precedent that we can utilize to access the C9 hydroxyl analogue from known bryostatin analogues. The only example of the synthesis of the bryostatin analogue with a C9 hemi-ketal through a direct C-H activation was reported by the Wender group (Scheme 3.1).[3] The DMDO oxidation converted analogue **3.1** into analogue **3.2** in good yield. The oxidation turned into highly regioselective given the fact there are five potential oxidation sites on compound **3.1**. Wender attributed the regioselectivtiy of DMDO oxidation to the conformation of analogue **3.1** and extraordinary selectivity of DMDO as a single oxygen transfer reagent. However, the

regioselectivity only applied to the special substrate **3.1**. The specialty of DMDO oxidation on analogue **3.1** prevents application to a wider variety of substituents.

Results And Discussion

In order to fit our need to diversify our bryostatin analogues, we decided to approach the bryostatin analogue with C9 hemi-ketal through a different route, which will allow us to install other functional groups in other sites. The first analogue target has C9 hemi-ketal and C13 olefin. The inclusion of the C13 olefin would allow us to construct the B ring via pyran annulation as in our previous syntheses of bryostatin analogues. The original retrosynthetic strategy to analogue **3.3** is outlined on Figure 3.2. Analogue **3.3** was to be prepared from intermediate seco acid **3.4**. The pyran annulation disconnection on the B ring leads to two intermediates, aldehyde **3.5** and hydroxyallylsilane **3.6**. The hydroxyallylsilane was to be prepared from ester **3.7** through the Bunnelle reaction. The construction of the ester was to be achieved by a cross metathesis between vinyl ketone **3.8** and terminal olefin **3.9**. Vinyl ketone **3.8** would be



Scheme 3.1 Wender's approach to bryostatin analogue with C9 hemi-ketal

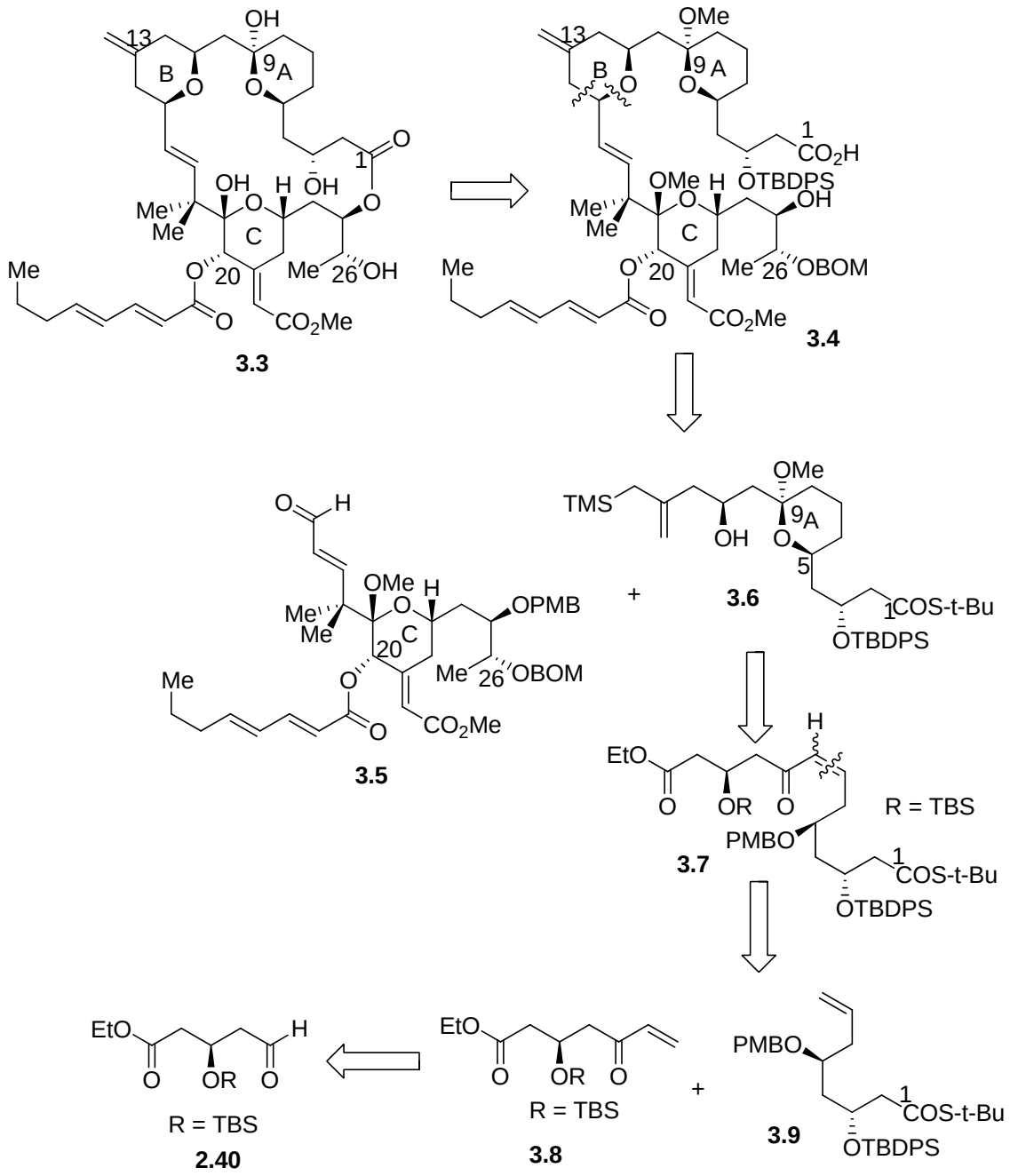


Figure 3.2 Original retrosynthesis of bryostatin analogue **3.3**

prepared from the known aldehyde **2.40**. Both aldehyde **2.40** and olefin **3.9** have been prepared in our previous syntheses of bryostatin analogues, which allows us to utilize the well-established routes to start the preparation of analogue **3.3**.

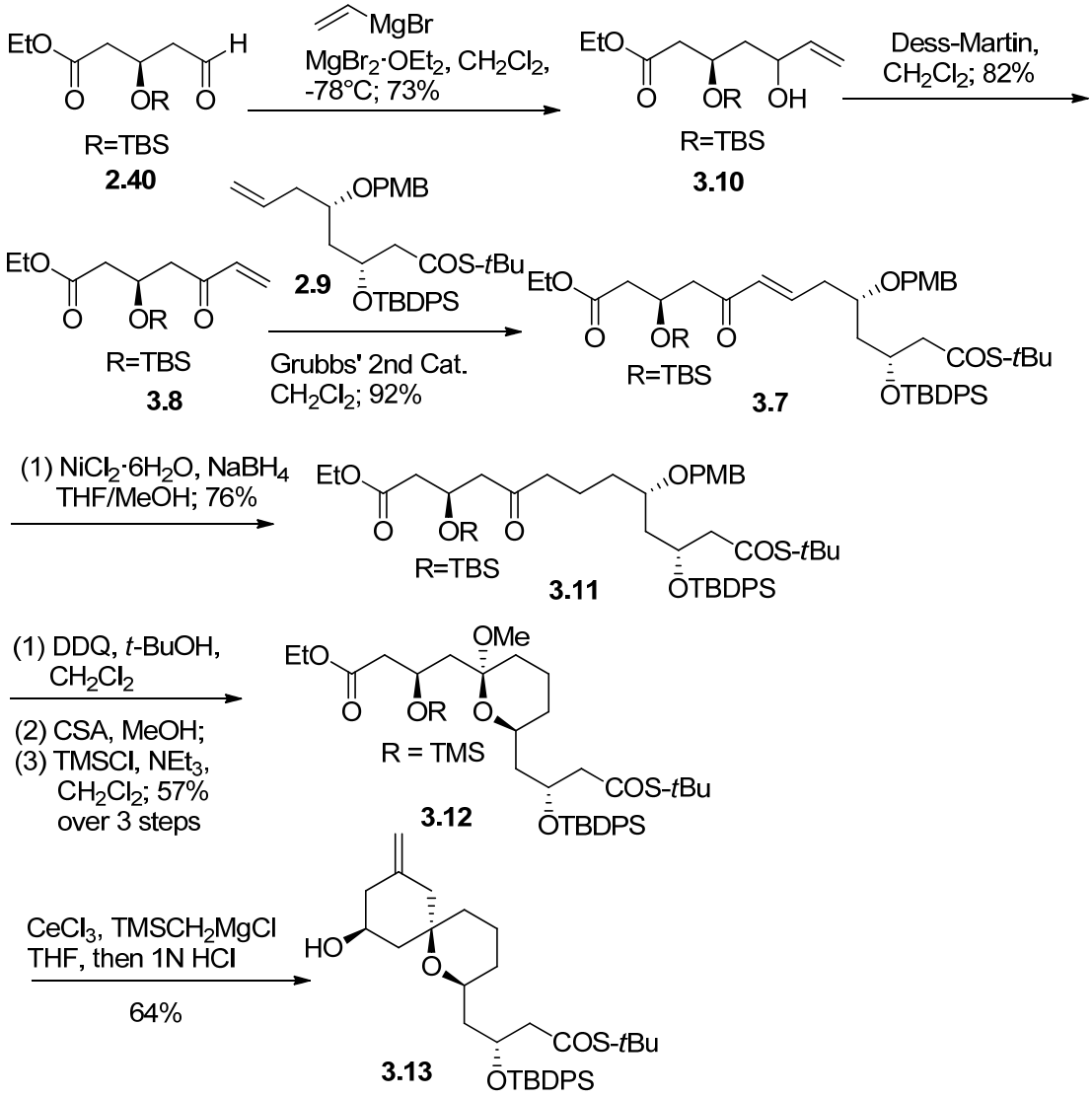
The synthesis of ester **3.7** started with aldehyde **2.40** (Scheme 3.2). The addition of vinyl magnesium bromide to aldehyde **2.40** at -78 °C afford the desired allylic alcohol **3.10** in good yield, which was oxidized by Dess-Martin periodinane to the vinyl ketone **3.8**. There was also starting material recovered from the Grignard reaction. Any attempt to push the reaction to completion by elevating the reaction temperature only resulted in the formation of six membered lactone via transesterification. In order to prevent the formation of the undesired lactone product, the Grignard reaction was kept at -78 °C, and the resulting alcohol was oxidized immediately after purification.

In the seminal report of Grubbs' study on the selectivity of cross metathesis reaction,[4] Grubbs classified olefin into four types: Type I olefins are categorized as those able to undergo a rapid homodimerization and the resulting homodimers can participate in cross metathesis as well as their terminal olefin counterpart, typical examples are terminal olefins and olefins with electron rich groups. Type II olefins homodimerize slowly, and unlike Type I olefins, their homodimers can only be sparingly consumed in subsequent metathesis reactions, α,β–unsaturated carbonyl compounds and sterically hindered allylic alcohol belong to this group; Type III olefins are essentially unable to be homodimerized by the catalyst but are still able to undergo cross metathesis with Type I and Type II olefins, this group include tri-substituted or all-substituted olefins, for which steric effects inhibit homodimerization. Type IV olefins are not able to participate in CM with a particular catalyst but do not inhibit catalyst activity toward other olefins.

The cross metathesis of type I with type II Olefins usually affords the *trans* product in high yield and stereoselectivity. Terminal olefin **3.9** as Type I and vinyl ketone **3.8** as Type II are perfect match for the cross metathesis reaction. The Grubbs reaction conditions, with a ratio of 1:2 for a Type I and Type II olefins, was able to deliver product **3.7** as exclusively the *E* diastereomer in quantitative yield. In order to limit the usage of terminal olefin **3.9**, the ratio was changed from 1:2 to 1:1.1, the cross metathesis still gave product **3.7** in 92% yield.

The chemoselective reduction of the C7-C8 double bond was achieved with $NaBH_4$ in the presence of $NiCl_2 \bullet 6H_2O$ in methanol. $NaBH_4$ reacted with $NiCl_2$ to generate nickel boride in situ,[5] which chemoselectively reduced the C7-C8 double bond to give ketone **3.11** with good yield. Attempts to effect this transformation via catalytic hydrogenation with Pd/C afforded a mixture of different reduced products. During the catalytic hydrogenation, both the PMB ether on C5 and thioester on C1 position were partially reduced as well.

With the ketone **3.11** in hand, our focus was transferred to forming the cyclic hemi-ketal and swapping the protecting group on the C11 position with TMS. The PMB group was removed with DDQ, and the resulting alcohol was subjected to reaction with CSA in methanol to afford the cyclic ketal. The TBS group on C11 position was also removed and the resulting free hydroxyl group was protected as the TMS ether to give product **3.12**. The application of Bunnelle reaction conditions to the ester **3.12** did not afford the desired hydroxyallylsilane; instead, a spiro ether product **3.13** was isolated after acidic work up. The formation of this spiro ether clear occurs through a tandem



Scheme 3.2 Failed route to hydroxyl allylsilane **3.6**

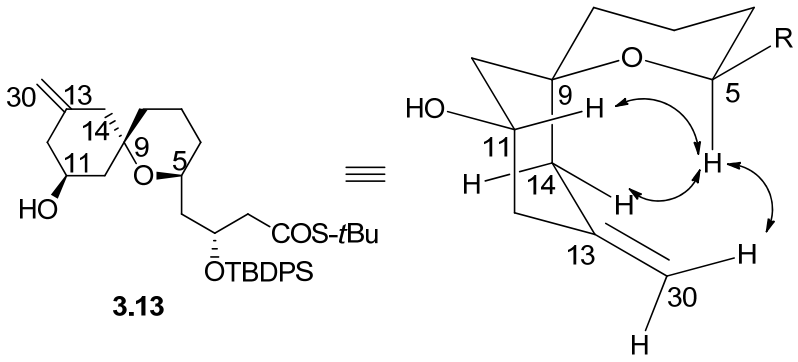
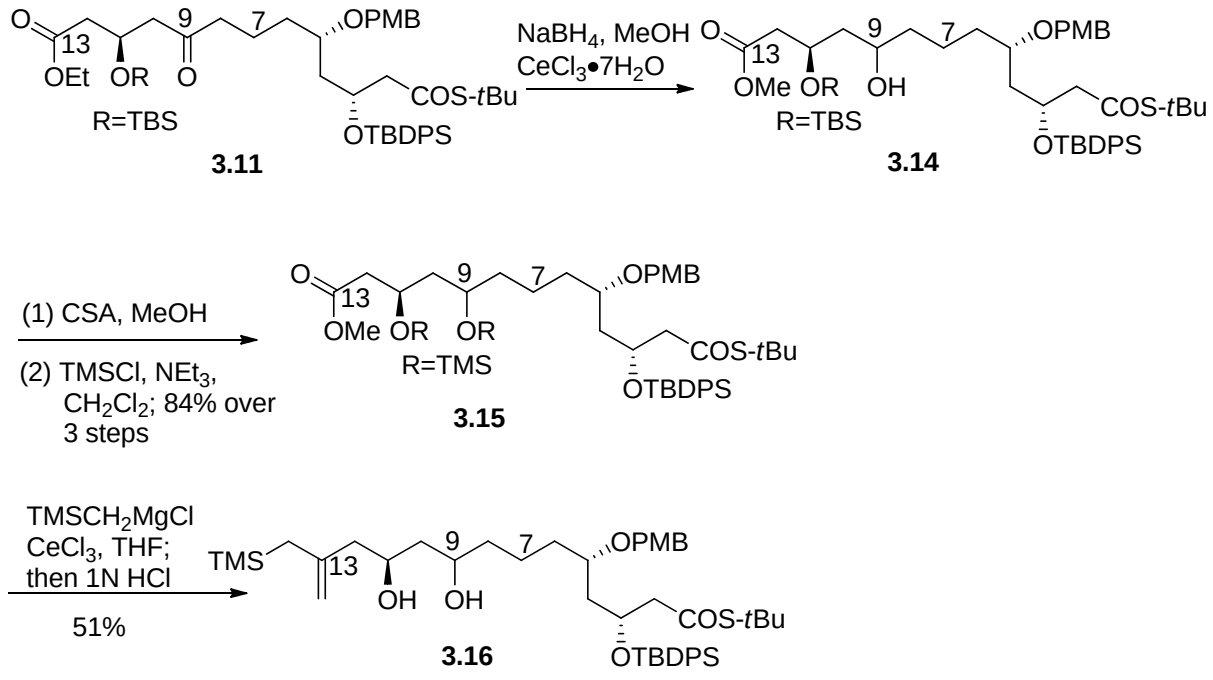


Figure 3.2 Confirmation of stereochemistry on C9 position of **3.13** by nOe

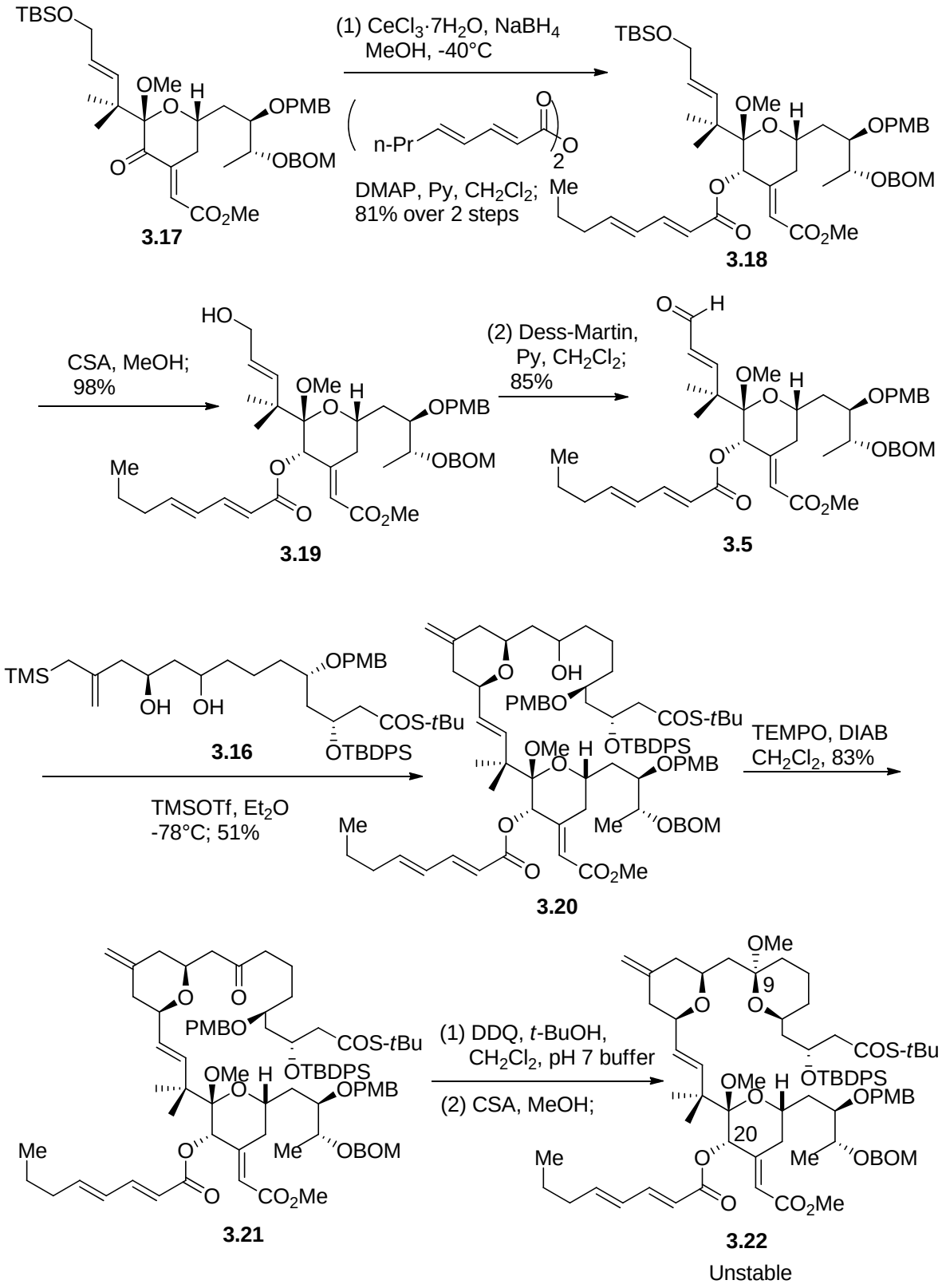
Peterson olefination/intramolecular Prins reaction. The stereochemistry at C9 in the product **3.13** was confirmed by the results from the nOe experiments (Figure 3.2).

This failure in preparation of the hydroxyallylsilane made us revise the route (Scheme 3.3). The ketone on the C9 position was reduced to give alcohol **3.14**, which will avoid the formation of an oxocarbenium ion during the acidic work up in the Bunnelle reaction. The TBS group on the C11 position was then swapped with TMS by deprotection with CSA and reprotection with TMSCl and NEt_3 in excellent yield. The ester **3.15** was then subjected to Bunnelle reaction conditions to deliver the desired hydroxyallylsilane **3.16** in modest yield.



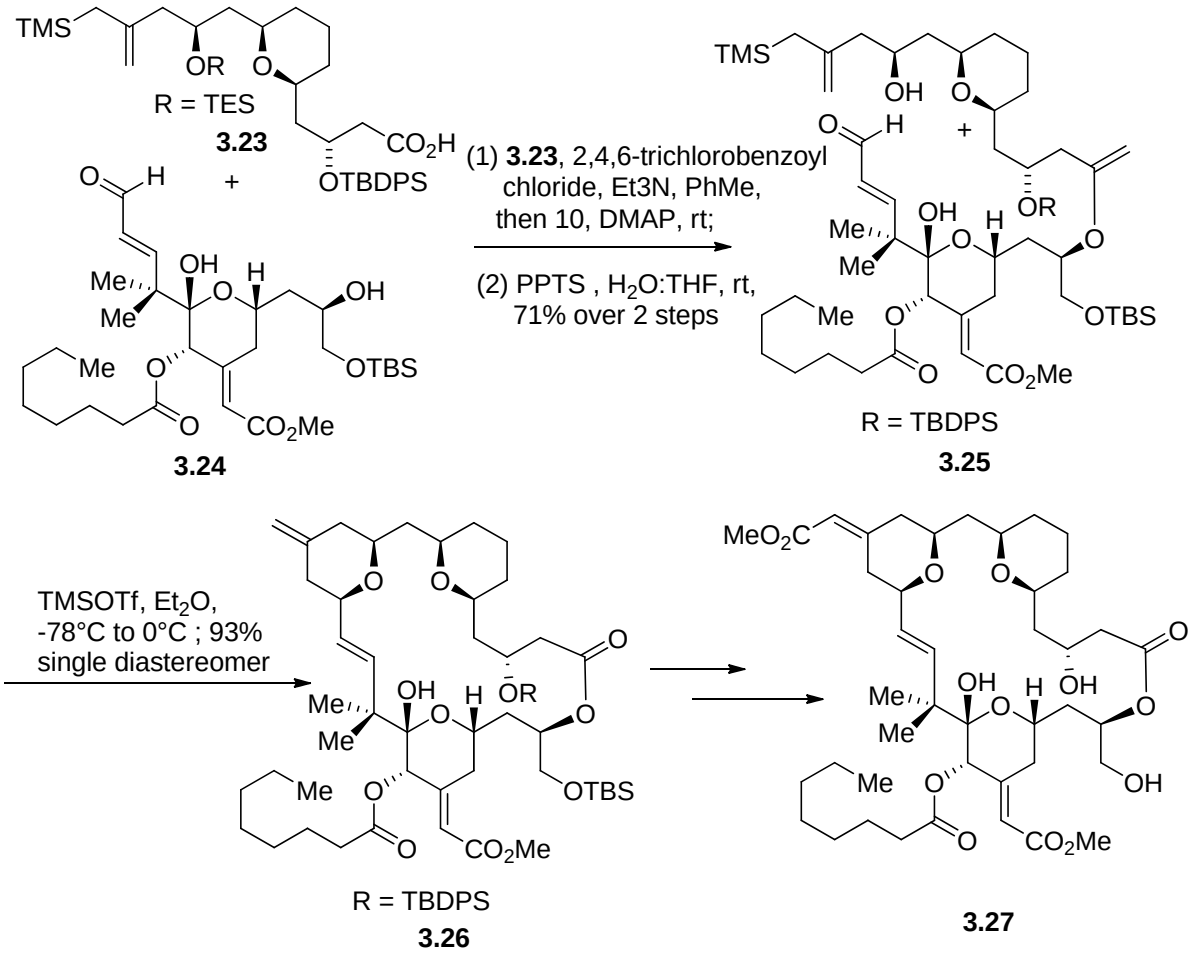
Scheme 3.3 Revised route to hydroxyl allylsilane **3.16**

After the completion of the synthesis of hydroxyl allylsilane **3.16**, we turned our attention into the aldehyde moiety **3.5**. Similar steps to those used previous were utilized to provide the fully functionalized C ring aldehyde **3.5** (Scheme 3.4). Ketone **3.17** was subjected to Luche reduction conditions to afford the alcohol, which was acylated to afford ester **3.18**. The natural unsaturated side chain of bryostatin 1 was installed on the C20 position. The TBS group in **3.18** was removed by CSA in methanol to afford the alcohol **3.19**. Dess-Martin periodinane converted the alcohol into aldehyde **3.5**. Finally, the pyran annulation between aldehyde **3.5** and hydroxyallylsilane **3.16** delivered the desired product **3.20** The oxidation of the C9 hydroxyl group in **3.20** with normal oxidation conditions such as TPAP/NMO, Dess-Martin periodinane, $SO_3 \cdot Py$/DMSO and $(COCl)_2$/DMSO did not provide any ketone product, only starting material was recovered from these reactions. The reluctance of the alcohol towards oxidation is most likely due to the complexity of the molecule and possible steric hindrance from nearby groups. Fortunately, the Goldman-Albright protocol successfully oxidized the secondary alcohol to give ketone **3.21** in excellent yield.[6] This solvent-free reaction has proved to be an efficient methodology to oxidize hindered secondary alcohol into ketone. We also found the TEMPO/DIAB condition could oxidize the alcohol **3.20** to the ketone in excellent yield.[7] This reaction was utilized due to ease of workup. Removal of the PMB group at C5 position with DDQ and treatment with CSA in methanol afforded the C9 ketal in good yield. Unfortunately, the product **2.22** was not stable, and underwent a hydrolysis on of the C9 ketal to release methanol. This unexpected problem prevented us from moving towards the final product given five more steps needed to complete the synthesis of our bryostatin analogue. An alternative route was needed to address this problem.



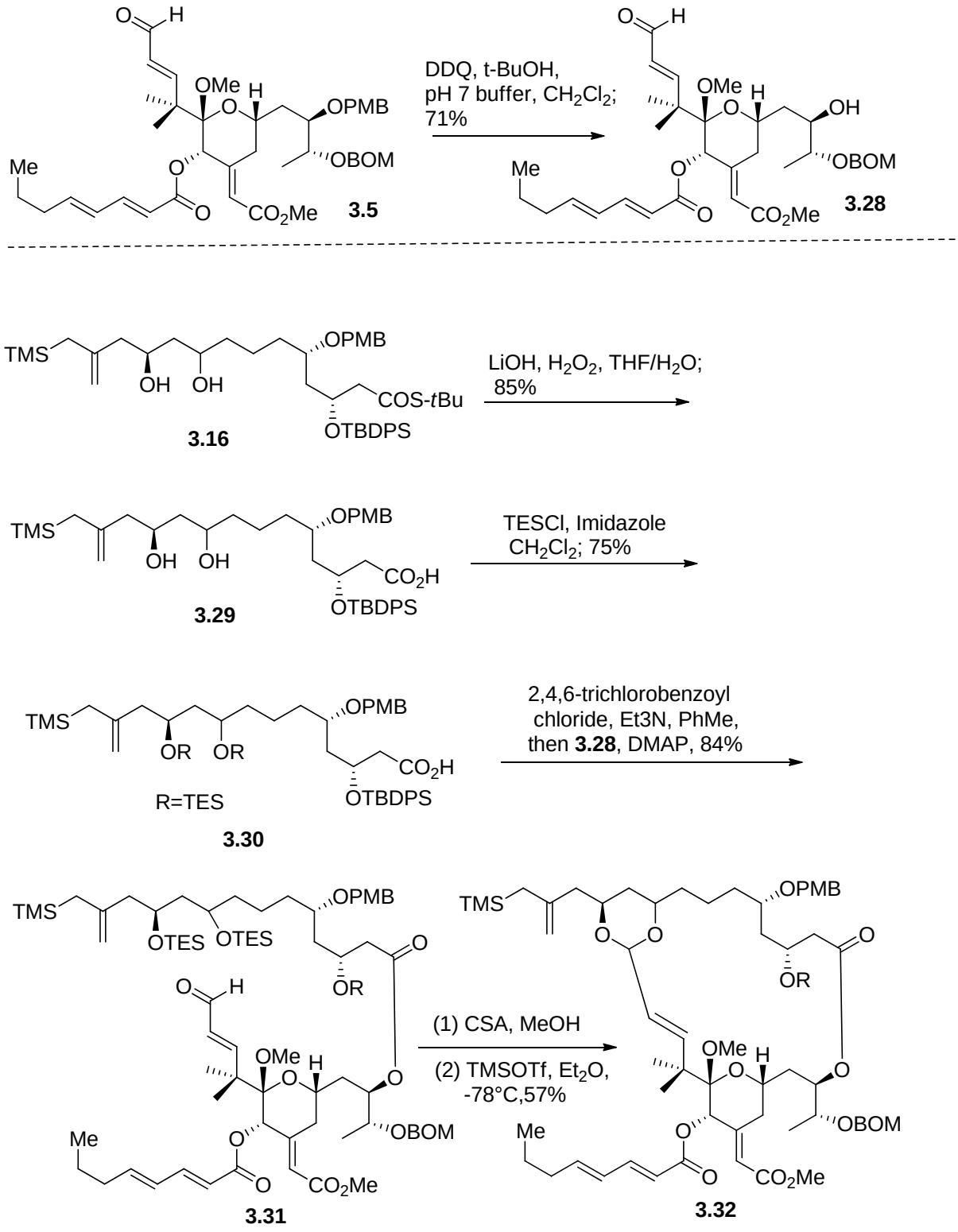
Scheme 3.4 Synthesis of unstable C9 ketal **3.22**

During Wender's synthesis of bryostatin analogue **3.27**. an intramolecular pyran annulation was chosen to cyclize the ring and form the macrolactone (Scheme 3.5). Yamaguchi reaction conditions were used to couple the carboxylic acid **3.23** and alchol **3.24** The TES group was removed regioselectively with PPTS to afford product **3.25** ready for pyran annulation. The intramolecular pyran annulation constructed the B ring and closed the ring into macrolactone **3.26** in excellent yield.[8]

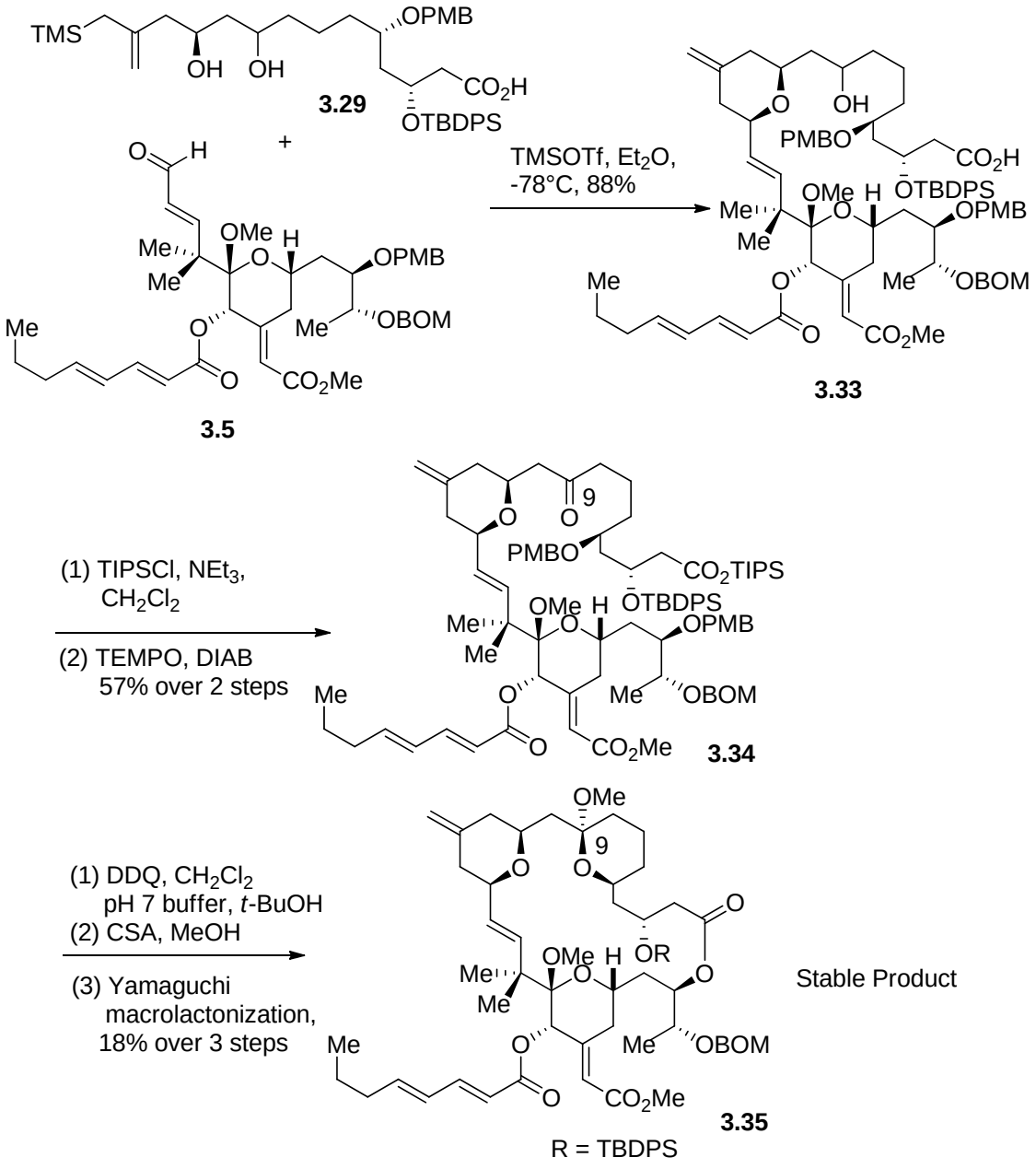


Scheme 3.5 Wender's synthesis of analogue **2.27** through an intramolecular pyran annulation

We envisioned that an intramolecular pyran annulation pathway would allow us to avoid the formation of the unstable C9 ketal before formation of the macrolactone. A revised route of intramolecular pyran annulation is outlined in Scheme 3.6. The PMB group on aldehyde **3.5** was removed with DDQ to afford the alcohol **3.28**. The thioester **2.16** was hydrolyzed by LiOH and H_2O_2, then the free hydroxyl groups on C9 and C11 were protected as TES ethers. The alcohol **3.27** and carboxylic acid **3.30** were coupled together by Yamaguchi reaction conditions, and the resulting ester **2.31** was exposed to CSA in methanol for the removal of the TES groups. The resulting substrate was subjected to TMSOTf for the pyran annulation. Unfortunately, the only product isolated after reaction is the acetal **3.32** rather than the desired B ring pyran. Attempts were made to force reaction from the acetal, but increasing temperature and increase in the amount of TMSOTf used did not promote the intramolecular Prins reaction to form the B ring pryan. It appears that the acetal embedded on this macrocylic framework is unusually stable. The failure of the desired intramolecular pyran annulation made us revisit the first route. Although the ketal **3.22** was not very stable at rt, it might survive if it was subjected to the Yamaguchi macrolactonization immediately after the preparation of ketal. In order to avoid the tedious steps of hydrolyzing thioester into carboxylic acid, we decided to hydrolyze the thioester before the pyran annulation (Scheme 3.7). This unprecedent pyran annulation between aldehyde **3.5** and hydroxyallylsilane **3.29** turned out to be a smooth reaction with excellent yield. The existence of carboxylic acid functional group in the hydroxyallylsilane unexpectedly improve the yield compared with the hydroxyallylsilane with thiolester moiety. The resulting product **3.33** was protected as silyl ester on C1 position. TEMPO/DIAB reaction conditions were chosen to oxidize the



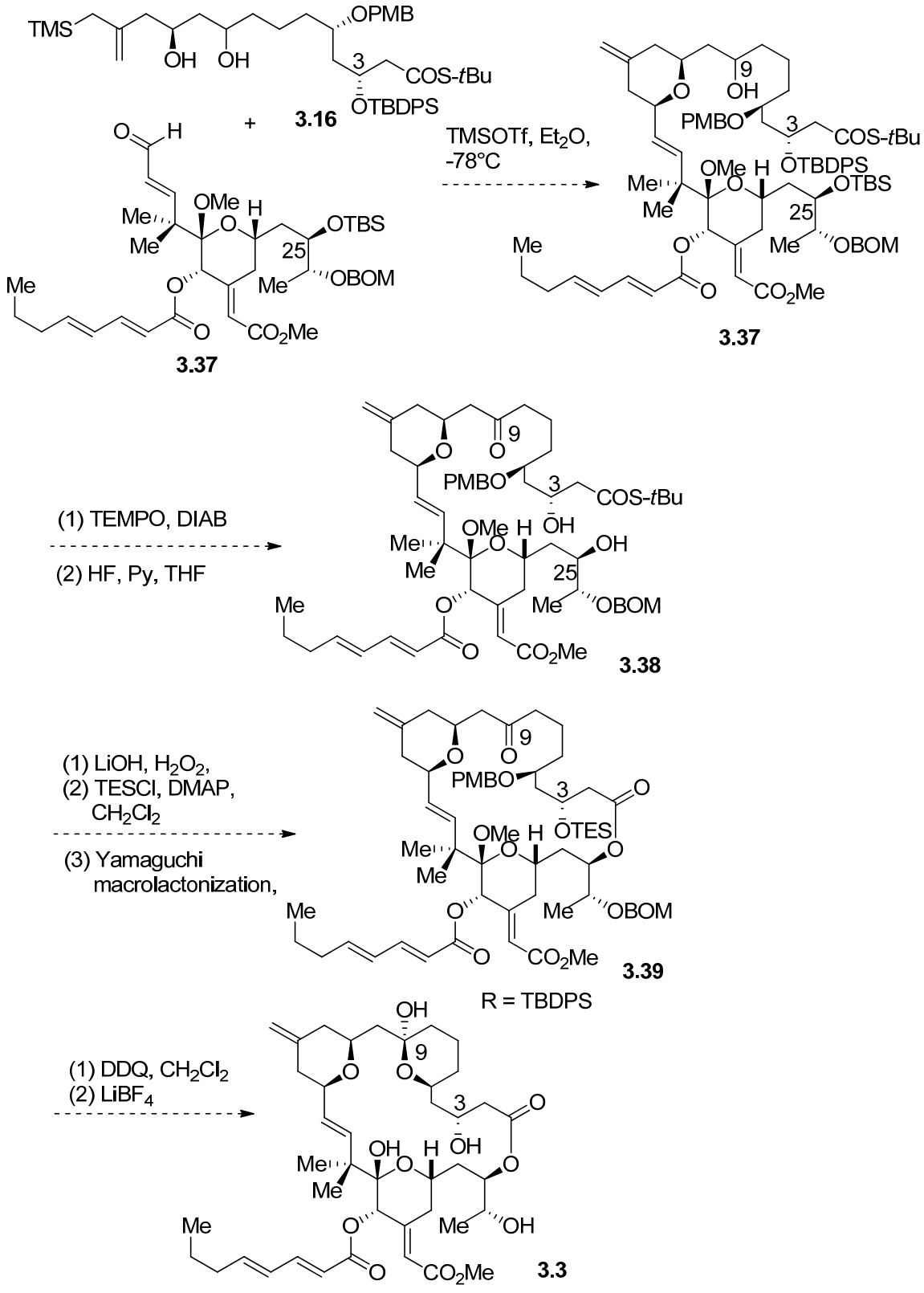
Scheme 3.6 The failed route of intramolecular pyran annulation



Scheme 3.7 Synthesis of macrolactone **2.35**

C9 hydroxyl group into ketone **3.34.** After the removal of the PMB group, treatment with CSA in methanol not only promoted the formation of the cyclic ketal, but also removed the TIPS group from C1, affording the seco acid ready for the cyclization. The crude seco acid was subjected to Yamaguchi reaction conditions immediately after work up, the desired product **3.35** was isolated after reaction with yield of 18% over three steps. The macrolactone product **3.35** was found to be stable.

The low yield of macrolactonization makes it really difficult to bring up enough material at this stage. Attempts to optimize this reaction conditions did not provide improved yield. The fact that the C9 ketal is not stable in open chain environment but stable in macrolactone suggests us that we should investigate formation of the ketal after macrolactonization. Based on this strategy, a new route has been designed and will be tested in future work. Firstly, in order to differentiate the protecting groups on the C25 position of the aldehyde with the C5 position of the hydroxyallylsilane, the PMB ether group at C25 was swapped for a TBS group, which will allow us to approach the seco acid without the problem of dealing with the C9 ketal. After the pyran annulation between aldehyde **3.36** and hydroxyallylsilane **3.16**, the free hydroxyl group on C9 of product **2.37** will be oxidized by TEMPO/DIAB. Both silyl groups will be removed with HF/Py to give diol **3.38**. The removal of the TBDPS group at C3 will ensure the regioselective hydrolysis of the thiolester under $LiOH/H_2O_2$ conditions.[9] The C3 free hydroxyl group will be reprotected with TESCl and DMAP, then the resulting seco acid will be subjected to Yamaguchi macrolactonization to afford the marcolactone **3.39**. The global deprotection will remove the remaining protecting groups and form the C9 hemi-ketal, affording the bryostatin analogue **3.3**.



Scheme 3.8 The future route to bryostatin analogue **3.3**

Conclusion

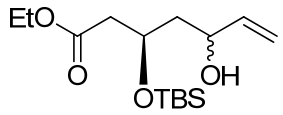
During our approach to the bryostatin analogue with C9 hemi-ketal, several routes were tested. The unstable C9 ketal in an open chain environment proved very frustrating and prevented us from preparing the final analogue product through our initial route. An intramolecuar pyran annulation strategy was designed to overcome the problem from the unstable C9 ketal. Unfortunately, the intramolcular pyran annulation failed to provide the desired product, instead only cyclized acetal product was isolated after reaction. The resistance of this acetal to react further was also surprising. Another attempt to cyclize the seco acid with the Yamaguchi protocol right after the formation of C9 ketal successfully delivered the desired macrolactone, but the low yield prevented us from acquiring enough material to the final product.

A revised route has been designed based on information gleaned from these studies and will be examined in the future. Moreover, in the course of this work, we explored the scope of pyran annulation with many different substrates. The results demonstrated that the pyran annulation reaction is versatile and flexible. It is also tolerant of functional groups such as hydroxyl and carboxylic acid. This methodology will be applied in our future research into the synthesis and biological characterization of bryostatin analogues.

Experimental Section

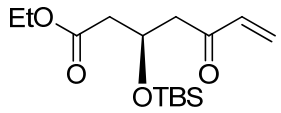
Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966).[10] Diisopropylamine, diisopropylethylamine, pyridine, triethylamine, EtOAc, MeOH, and CH_2Cl_2 were distilled from CaH_2. The titer of *n*-BuLi was determined by the method of Eastham and Watson.[11] All other reagents were used without further purification. Yields were calculated for material judged homogenous by thin layer chromatography and nuclear magnetic resonance (NMR). Thin layer chromatography was performed on Merck Kieselgel 60 Å F254 plates or Silicycle 60 Å F254 eluting with the solvent indicated, visualized by a 254 nm UV lamp, and stained with an ethanolic solution of 12-molybdophosphoric acid, or 4-anisaldehyde. Flash column chromatography was performed with Silicycle Flash Silica Gel 40 – 63 μm or Silicycle Flash Silica Gel 60 – 200 μm, slurry packed with 1% EtOAc/hexanes in glass columns. Glassware for reactions was oven dried at 125 °C and cooled under a dry nitrogen atmosphere prior to use. Liquid reagents and solvents were introduced by oven dried syringes through septum-sealed flasks under a nitrogen atmosphere. Nuclear magnetic resonance spectra were acquired at 500 MHz for ^1H and 125 MHz for ^{13}C. Chemical shifts for proton nuclear magnetic resonance (^1H NMR) spectra are reported in parts per million relative to the signal of residual $CHCl_3$ at 7.27 ppm. Chemicals shifts for carbon nuclear magnetic resonance (^{13}C NMR and DEPT) spectra are reported in parts per million relative to the center line of the $CDCl_3$ triplet at 77.23 ppm. Chemical shifts of the unprotonated carbons ('CH_0') for DEPT spectra were obtained by comparison with the ^{13}C NMR spectrum. The abbreviations s, d, apd, dd, ddd, dddd, ddddd, dddddd, t, td, tt, q, dq, and m stand for the

resonance multiplicity singlet, doublet, apparent doublet, doublet of doublets, doublet of doublet of doublets, doublet of doublet of doublet of doublets, doublet of doublet of doublet of doublets of doublets, doublet of doublet of doublet of doublets of doublets of doublets, triplet, triplet of doublets, triplet of triplets, quartet, doublet of quartets, and multiplet, respectively. Optical rotations (Na D line) were obtained using a microcell with 1 dm path length. Specific rotations ([α], Unit: °cm^2/g) are based on the equation $\alpha = (100 \cdot \alpha)/(l \cdot c)$ and are reported as unit-less numbers where the concentration *c* is in g/l00 mL and the path length *l* is in decimeters. Mass spectrometry was performed at the mass spectrometry facility of the Department of Chemistry at The University of Utah on a double focusing high resolution mass spectrometer. Compounds were named using ChemDraw 12.0.



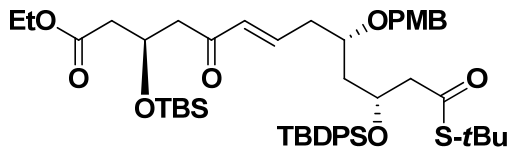
Preparation of (*R*)-ethyl 3-(tert-butyldimethylsilyloxy)-5-hydroxyhept-6-enoate (3.10). To a stirring solution of aldehyde **2.40** (255.8 mg, 0.9321 mmol, 1.0 equiv) in CH_2Cl_2 (18.6 mL, 0.05 M) in a 50 mL rb flask at rt was added $MgBr_2 \cdot OEt_2$ (481.4 mg, 1.864 mmol, 2.0 equiv) in one portion. The mixture was stirred at rt for 5 min, then cooled to -78 °C. The mixture was stirred at -78 °C for 5 min, and then a solution of vinyl magnesium bromide (1.40 mL of 1.0M, 1.40 mmol, 1.5 equiv) was added via syringe. The mixture was stirred at -78 °C for 2 h before being quenched by the addition of saturated aqueous NH_4Cl solution (20 mL). The mixture was warmed to rt, and the aqueous phase was separated and extracted with CH_2Cl_2 (3 × 40 mL). The organic phases

were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 19 cm column, eluting with 10% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (17-23) were combined and concentrated under reduced pressure to give the product **3.10** (206.0 mg, 73%) as a colorless oil: R_f = 0.41 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +5 (*c* = 0.08, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 5.87 (ddd, *J* = 17.1, 10.3, 5.9 Hz, 1H), 5.29 (t, *J* = 1.5 Hz, 1H), 5.25 (t, *J* = 1.5 Hz, 1H), 4.36-4.27 (m, 2H), 4.16-4.09 (m, 2H), 2.60 (d, *J* = 2.9 Hz, 1H), 2.56 (t, *J* = 5.9 Hz, 2H), 1.82-1.70 (m, 2H), 1.26 (t, *J* = 7.3 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 171.6, 140.9, 114.6, 71.0, 68.7, 60.7, 44.1, 43.2, 25.9, 18.1, 14.4, -4.3, -4.5; 125 MHz DEPT ($CDCl_3$) CH_3 δ 25.9, 14.4, -4.3, -4.5; CH_2 δ 114.6, 60.7, 44.1, 43.2; CH δ 140.9, 71.0, 68.7; CH_0 δ 171.6, 18.1; IR (neat) 3509, 2978, 2955, 2930, 2897, 2856, 1736, 1464, 1410, 1376, 1309, 1254, 1209, 1175, 1085, 1032, 960, 923, 836, 808, 776, 752, 667 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{49}H_{72}NaO_8Si_2S$ (M+Na) 325.1811, found 325.1817.



Preparation of (*R*)-ethyl 3-(*tert*-butyldimethylsilyloxy)-5-oxohept-6-enoate (3.8). To a solution of alcohol **3.10** (206.0 mg, 0.6810 mmol, 1.0 equiv) in CH_2Cl_2 (6.8 mL, 0.1 M) in a 25 mL rb flash at rt was added Dess-Martin periodinane (433.3 mg, 1.022 mmol, 1.5 equiv) in one portion. The reaction mixture was stirred at rt overnight, and then quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution (10 mL). The

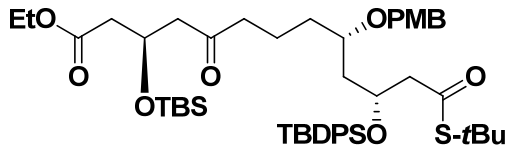
mixture was stirred at rt until the whole solution turned clear, the aqueous phase was separated and extracted with CH_2Cl_2 for (3 × 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 14 cm column, eluting with 10% EtOAc/hexanes (500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (6-8) were combined and concentrated under reduced pressure to give the product **3.8** (168.1 mg, 82%) as a colorless oil: R_f = 0.60 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = +7.4 (*c* = 1.72, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 6.36 (dd, *J* = 17.6, 10.3 Hz, 1H), 6.24 (d, *J* = 17.6 Hz, 1H), 5.87 (d, *J* = 11.7 Hz, 1H), 4.63 (dddd, *J* = 11.7, 5.9, 5.9, 5.9 Hz, 1H), 4.18-4.08 (m, 2H), 2.90 (dd, *J* = 15.6, 6.8 Hz, 1H), 2.81 (dd, *J* = 15.6, 6.4 Hz, 1H), 2.55 (dd, *J* = 15.1, 5.9 Hz, 1H), 2.49 (dd, *J* = 14.6, 5.9 Hz, 1H), 1.26 (t, *J* = 7.3 Hz, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 199.0, 171.2, 137.4, 128.9, 66.2, 60.6, 47.0, 42.9, 25.9, 18.1, 14.4, -4.6, -4.7; 125 MHz DEPT ($CDCl_3$) CH_3 δ 25.9, 14.4, -4.6, -4.7; CH_2 δ 128.9, 60.6, 47.0, 42.9; CH δ 137.4, 66.2; CH_0 δ 199.0, 171.2, 18.1; IR (neat) 2933, 2858, 1737, 1685, 1615, 1468, 1375, 1255, 1195, 1092, 965, 778, 665 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{15}H_{28}NaO_4Si$ (M+Na) 323.1655, found 323.1655.



Preparation of (3*R*,9*S*,11*R*,*E*)-ethyl 3-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyldi phenyl silyloxy)-13-(*tert*-butylthio)-9-(4-methoxybenzyloxy)-5,13-dioxotridec -6-enoate (3.7). To a solution of vinyl ketone **3.8** (168.1 mg, 0.5595 mmol, 1.1 equiv)

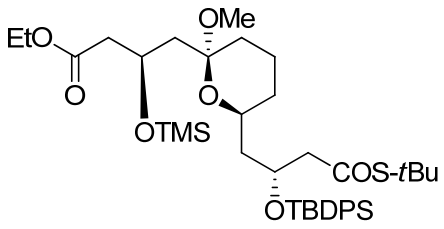
and olefin **3.9** (307.7 mg, 0.5086 mmol, 1.0 equiv) in CH_2Cl_2 (28 mL, 0.019 M) in a 50 mL rb flask at rt was added Grubbs' 2nd generation catalyst (21.6 mg, 0.0254 mmol, 0.05 equiv) in one portion. Then the flask was equipped with a condenser, and the reaction mixture was heated to reflux and kept overnight. The mixture was cooled to rt and the solvent was removed under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 19 cm column, eluting with 10% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (13-26) were combined and concentrated under reduced pressure to give the product **3.7** (412.1 mg, 92%) as a brown oil: R_f = 0.54 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = -12 (*c* = 0.23, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) ^{1}H NMR ($CDCl_3$) δ 7.72-7.66 (m, 4H), 7.45-7.35 (m, 6H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.65 (ddd, *J* = 15.6, 7.4, 7.3 Hz, 1H), 6.00 (d, *J* =16.1 Hz, 1H), 4.63 (dddd, *J* = 12.2, 6.4, 6.4, 6.4 Hz, 1H), 4.36 (dddd, *J* = 12.2, 6.4, 6.4, 6.4 Hz, 1H), 4.22 (d, *J* = 11.2 Hz, 1H), 4.18-4.10 (m, 2H), 4.05 (d, *J* = 10.7 Hz, 1H), 3.40 (dddd, *J* = 9.8, 5.4, 5.4, 5.4 Hz, 1H), 2.78 (dd, *J* = 15.6, 6.3 Hz, 1H), 2.71 (dd, *J* = 10.3, 5.9 Hz, 1H), 2.68 (dd, *J* = 10.3, 5.9 Hz, 1H), 2.68 (dd, *J* = 10.3, 5.9 Hz, 1H), 2.61 (dd, *J* = 14.7, 6.3 Hz, 1H), 2.46 (dd, *J* = 14.6, 6.3 Hz, 1H), 1.80 (ddd, *J* = 14.2, 7.8, 5.4 Hz, 1H), 1.58 (ddd, *J* = 14.2, 6.5, 4.4 Hz, 1H), 1.42 (s, 9H), 1.26 (t, *J* = 7.3Hz, 3H), 1.03 (s, 9H), 0.84 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 198.0, 197.7, 171.2, 159.2, 143.9, 136.1, 136.1, 134.0, 133.7, 133.2, 130.5, 130.0, 129.9, 129.4, 127.8, 113.9, 74.9, 70.6, 68.8, 66.2, 60.6, 55.4, 52.9, 48.2, 47.3, 42.9, 42.8, 37.5, 29.9, 27.1, 25.9, 19.6, 18.1, 14.4, -4.5, -4.8; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 29.9, 27.1, 25.9, 14.4, -4.5, -4.8; CH_2 δ 70.6, 60.6, 52.9, 47.3, 42.9, 42.8, 37.5; CH δ 143.9, 136.1, 136.1, 133.2, 130.0, 129.9, 129.4, 127.8, 113.9, 74.9, 68.8, 66.2; CH_0 δ 198.0, 197.7,

171.2, 159.2, 134.0, 133.7, 130.5, 48.2, 19.6, 18.1; IR (neat) 2931, 2858, 1736, 1679, 1615, 1464, 1427, 1365, 1302, 1250, 1174, 1107, 830, 778, 740, 704, 590, 536 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{49}H_{72}NaO_8Si_2S$ (M+Na) 899.4384, found 899.4379.



Preparation of (3*R*,9*R*,11*R*)-ethyl 3-(*tert*-butyldimethylsilyloxy)-11-(*tert*-butyl di phenyl silyloxy)-13-(butylthio)-9-(4-methoxybenzyloxy)-5,13-dioxotridecanoate (3.11). To a stirring solution of unsaturated ketone **3.7** (207.9 mg, 0.2370 mmol, 1.0 equiv) in THF/MeOH (1:4) (1.8 mL, 7.9 mL, 0.03 M) in a 50 mL rb flask at 0 °C was added $NiCl_2 \cdot 6H_2O$ (28.2 mg, 0.119 mmol, 0.5 equiv). Once the crystals had dissolved, $NaBH_4$ (17.9 mg, 0.4740 mmol, 2.0 equiv) was added portionwise. The color of the solution changed from light green to dark brown quickly. After the addition of $NaBH_4$, the reaction mixture was stirred at 0 °C for 1 h, and then quenched by the addition of 1N HCl (0.6 mL). After 5 min at 0 °C, the mixture was transferred into a separatory funnel with 50% EtOAc/hexanes (20 mL). The aqueous phase was separated and extracted with 50% EtOAc/hexanes (3 × 20 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 14 cm column, eluting with 10% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (10-22) were combined and concentrated under reduced pressure to give the product **3.12** (158.4 mg, 76%) as a colorless oil: R_f = 0.54 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = -15.2 (*c* = 0.57, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.73-7.67 (m, 4H), 7.44-7.35 (m, 6H), 7.12 (d, *J* =

8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.57 (dddd, *J* = 6.4, 5.9, 5.9, 5.9 Hz, 1H), 4.35 (dddd, *J* = 6.4, 6.4, 5.9, 5.9 Hz, 1H), 4.22 (d, *J* = 10.7 Hz,1H), 4.15-4.10 (m, 2H), 4.06 (d, *J* = 10.7 Hz, 1H), 3.80 (s, 3H), 3.30-3.22 (m, 1H), 2.70 (dd, *J* = 14.7, 6.3 Hz, 1H), 2.64 (dd, *J* = 16.1, 6.8 Hz, 1H), 2.62 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.57 (dd, *J* = 15.6, 5.4 Hz, 1H), 2.47 (dddd, *J* = 14.7, 14.7, 14.7, 5.9 Hz, 2H), 2.27 (dd, *J* =7.8, 6.8 Hz, 2H), 1.79 (ddd, *J* = 13.7, 7.3, 5.9 Hz, 1H), 1.56 (ddd, *J* = 10.8, 5.9, 4.4 Hz, 1H), 1.41 (s, 9H), 1.28 (t, *J* = 6.8 Hz, 3H), 1.02 (s, 9H), 0.85 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 208.7, 197.9, 171.2, 159.1, 136.1, 136.1, 134.1, 133.9, 131.0, 129.8, 129.8, 129.4, 127.8, 113.8, 75.6, 70.1, 69.0, 65.9, 60.6, 55.4, 52.8, 49.9, 48.1, 44.3, 42.7, 42.4, 33.5, 29.9, 27.1, 25.9, 19.6, 19.0, 18.1, 14.4, -4.6, -4.8; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 29.9, 27.1, 25.9, 14.4, -4.6, -4.8; CH_2 δ 70.1, 60.6, 52.8, 49.9, 44.3, 42.7, 42.4, 33.5, 19.0; CH δ 136.1, 136.1, 129.8, 129.8, 129.4, 127.8, 113.8, 75.6, 69.0, 65.9; CH_0 δ 208.7, 197.9, 171.2, 159.1, 134.1, 133.9, 131.0, 48.1, 19.6, 18.1; IR (neat) 3070, 2955, 2858, 1735, 1682, 1613, 1588, 1513, 1463, 1427, 1366, 1301, 1250, 1175, 1108, 1037, 832, 778, 740, 705, 611, 536, 509 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{49}H_{74}NaO_8Si_2S$ (M+Na) 901.4541, found 901.4537.



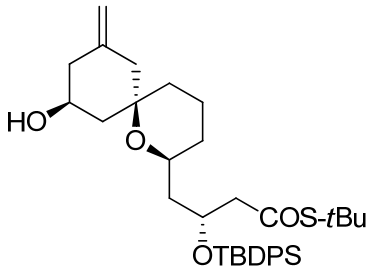
Preparation of (*R*)-ethyl 4-((2*R*,6*S*)-6-((*R*)-2-((*tert*-butyldiphenylsilyl)oxy)-4-(*tert*-butylthio)-4-oxobutyl)-2-methoxytetrahydro-2H-pyran-2-yl)-3-((trimethylsilyl) oxy) butanoate (3.12). To a stirring solution of PMB ether **3.11** (238.0 mg, 0.2707mmol,

1.0 equiv) in CH_2Cl_2 (50 mL, 0.005 M) in a 100 mL rb flask at 0 ºC were added *tert*-butyl alcohol (4.3 mL), aqueous pH 7 buffer (4.3 mL), and DDQ (185 mg, 0.8121 mmol, 3.0 equiv). The reaction mixture was stirred at 0 ºC for 2 h and additional DDQ (185 mg, 0.8121 mmol, 3.0 equiv) was then added. Stirring was continued for 1.5 h and the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). After stirring vigorously for 10 min at rt, the aqueous phase was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was taken on to the next step without purification.

To a 25 mL rb flask containing the aforementioned alcohol in methanol (9.0 mL, 0.03 M) at 0 ºC was added CSA (113.2 mg, 0.4873 mmol, 1.8 equiv) in one portion. The reaction mixture was stirred at 0 ºC for 5 h, and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous phase was separated and extracted with 50% EtOAc/hexanes (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was taken on to the next step without purification.

To a 25 mL rb flask containing the aforementioned alcohol in CH_2Cl_2 (9.0 mL, 0.03 M) at 0 ºC was added NEt_3 (274.1 mg, 2.708 mmol, 10 equiv) and TMSCl (147.0 mg, 1.354 mmol, 5 equiv) via syringe. After 12 h at rt, the mixture was quenched by the addition of water (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 18 cm silica gel column, eluting with 5%

EtOAc/hexanes (1000 mL), collecting 25 mL fractions. The product containing fractions (11-18) were combined and concentrated under reduced pressure to provide silyl ether **3.12** (96.9 mg, 57% over three steps) as a colorless oil: R_f = 0.68 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = + 2.2 (*c* = 1.47, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.66 (m, 4H), 7.45-7.35 (m, 6H), 4.34-4.27 (m, 1H), 4.27-4.21 (m, 1H), 4.16 (dddd, *J* = 10.8, 7.3, 7.3, 7.3 Hz, 1H), 4.10 (dddd, *J* = 11.2, 7.3, 7.3, 7.3 Hz, 1H), 3.27-3.21 (m, 1H), 3.00 (s, 3H), 2.76 (dd, *J* = 14.7, 4.4 Hz, 1H), 2.70 (dd, *J* = 14.7, 7.3 Hz, 1H), 2.59 (dd, *J* = 15.1, 7.3 Hz, 1H), 2.36 (dd, *J* = 15.1, 7.3 Hz, 1H), 1.76 (dd, *J* = 14.2, 6.4 Hz, 1H), 1.70 (dd, *J* = 14.7, 5.9 Hz, 1H), 1.64-1.54 (m, 3H), 1.45 (s, 9H), 1.45-1.38 (m, 4H), 1.27 (t, *J* = 6.8 Hz, 3H), 1.10 (d, *J* = 11.3 Hz, 1H), 1.04 (s, 9H), 0.10 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ 198.2, 171.9, 136.2, 136.1, 134.6, 134.0, 129.9, 129.8, 127.8, 127.7, 98.5; 125 MHz DEPT ($CDCl_3$) CH_3 δ 47.7, 30.0, 27.2, 14.5, 0.5; CH_2 δ 60.4, 53.2, 44.3, 44.0 (× 2), 32., 30.9, 18.8; CH δ 136.2, 136.1, 129.9, 129.8, 127.8, 127.7, 69.7, 68.1, 66.5; CH_0 δ 198.2, 171.9, 134.6, 134.0, 98.5, 48.1, 19.6; IR (neat) 3072, 2955, 2853, 1735, 1682, 1613, 1588, 1515, 1463, 1427, 1366, 1321, 1250, 1175, 1108, 1037, 832, 778, 740, 705, 611, 536, 509 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{39}H_{62}NaO_7Si_2$ (M+Na) 753.3653, found 753.3657.



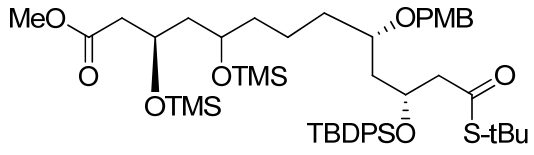
Preparation of (3R)-S-*tert*-butyl 3-((*tert*-butyldiphenylsilyl)oxy)-4-((2S,8S)-8-hydroxy-10-methylene-1-oxaspiro[5.5]undecan-2-yl)butanethioate (3.13). Powdered

$CeCl_3 \cdot 7H_2O$ (917.3 mg, 2.462 mmol, 10.0 equiv) was placed in a 25 mL rb flask and heated to 170 ºC under 1 mm Hg vacuum. After 16 h at 170 ºC, the dried $CeCl_3$ was cooled to rt, and the flask was purged with N_2. THF (2.5 mL) was added, and the mixture was stirred at rt for 2 h.

Meanwhile, a 25 mL three-necked rb flask equipped with condenser and magnetic stir bar was charged with magnesium turnings (124.0 mg, 5 mmol, 1.0 equiv), and a crystal of iodine. The flask was heated with a heat gun for 5 min while stirring. THF (5.0 mL) was added via syringe, and the reaction mixture was heated with the heat gun to reflux. Chloromethyl trimethylsilane (0.613 g, 5.0 mmol, 1.0 equiv) was then added dropwise via syringe. The mixture was stirred at rt for 1.5 h to give an assumed 1.0 M solution of $TMSCH_2MgCl$.

The $CeCl_3$/THF mixture was cooled to -78 ºC, and then a solution of $TMSCH_2MgCl$ (2.46 mL, 2.46 mmol, 10.0 equiv) was added dropwise via syringe. After 1 h at -78 ºC, ester **3.12** (180.0 mg, 0.2462 mmol, 1.8 equiv) in THF (1.0 mL) was added via cannula. An additional THF (0.6 mL) rinse was used to transfer the remaining ester residue into the reaction mixture. The solution was allowed to warm to rt and stirred overnight. The mixture was then cooled to -78 ºC, and then was quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The reaction mixture was then allowed to warm to rt and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 30 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in THF (10 mL), and the resulting solution was cooled to 0 ºC. Two drops of 1N HCl solution was added into flask with pipette. After 5 min at 0 ºC, the reaction mixture was quenched by the addition of

saturated aqueous $NaHCO_3$ solution (2 mL). The reaction mixture was then allowed to warm to rt and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 12 cm column, eluting with 20% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (19-22) were combined and concentrated under reduced pressure to give the product **3.13** (93.6 mg, 64%) as a colorless oil: R_f = 0.24 (20% EtOAc/hexanes); $[\alpha]_D^{20}$ = -17.3 (*c* = 2.21, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) ^{1}H NMR ($CDCl_3$) δ 7.73-7.66 (m, 4H), 7.46-7.35 (m, 6H), 4.75 (s, 1H), 4.55 (s, 1H), 4.24-4.17 (m, 1H), 4.00-3.92 (m, 1H), 3.04-2.97 (m, 1H), 2.88 (dd, *J* = 15.1, 3.4 Hz, 1H), 2.71 (d, *J* = 14.2, Hz, 1H), 2.65 (dd, *J* = 15.6, 8.3 Hz, 1H), 2.58 (dd, *J* = 12.2, 4.8 Hz, 1H), 1.93 (d, *J* = 11.7 Hz, 1H), 1.89-1.84 (m, 1H), 1.60-1.50 (m, 3H), 1.47 (s, 9H), 1.47-1.42 (m, 2H), 1.32-1.24 (m, 6H), 1.10 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) 198.4, 142.5, 136., 126.1, 135.0, 124.0, 129.8, 129.6, 127.7, 127.6, 112.3, 74.7, 70.2, 67.6, 53.2, 48.7, 47.9, 44.7, 44.2, 37.8, 35.8, 32.0, 30.1, 27.2, 19.6, 19.4; 125 MHz DEPT ($CDCl_3$) CH_3 δ 30.1, 27.2; CH_2 δ 112.3, 53.2, 48.7, 44.7, 44.2, 37.8, 35.8, 32.0, 19.4; CH δ 136.2, 136.1, 129.8, 129.6, 127.7, 127.6, 70.2, 67.6, 67.3; CH_0 δ 198.4, 142.5, 135.0, 134.0, 74.7, 47.9, 19.6; IR (neat) 2954, 2853, 1741, 1681, 1611, 1513, 1430, 1364, 1331, 1250, 1168, 1108, 1038, 841, 744, 704, 610, 536 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{35}H_{50}O_4SiSNa$ (M+Na) 617.3097, found 617.3101.

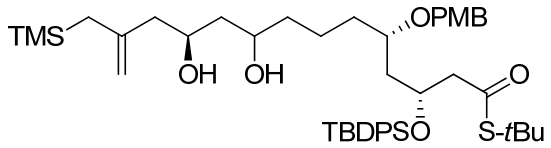


Preparation of (3*R*,9*S*,11*R*)-methyl 11-(*tert*-butyldiphenylsilyloxy)-13-(*tert*-butylthio)-9-(4-methoxybenzyloxy)-13-oxo-3,5-bis(trimethylsilyloxy)tridecanoate (3.15). To a stirring solution of ketone **3.14** (220.2 mg, 0.2504 mmol, 1.0 equiv) in MeOH (12.5 mL, 0.02 M) at rt was added $CeCl_3 \cdot 7H_2O$ (46.6 mg, 0.1252 mmol, 0.5 equiv) in one portion. The mixture was stirred at rt until all crystals had dissolved. Then the solution was cooled to 0 °C, $NaBH_4$ (18.9 mg, 0.5008 mmol, 2.0 equiv) was added in one portion, and the mixture was stirred at 0 °C for 15 min and then quenched by the addition of saturated aqueous NH_4Cl solution (2 mL). The mixture was extracted with 50% EtOAc/hexanes (3 × 25mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was carried into the next step without purification.

To a stirring solution of the aforementioned intermediate alcohol (0.2504 mmol, 1.0 equiv) in MeOH (12.5 mL, 0.02 M) at 0 °C was added CSA (116.3 mg, 0.5008 mmol, 2.0 equiv) in one portion. The solution was stirred at 0 °C for 5 h, and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (10 mL). The mixture was then extracted with 50% EtOAc/hexanes (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product was carried into the next step without purification.

To a stirring solution of the aforementioned intermediate alcohol (0.2504 mmol, 1.0 equiv) in CH_2Cl_2 (12.5 mL, 0.02 M) at rt in a 50 mL rb flask was added NEt_3 (506.7 mg, 5.008 mmol, 20 equiv) and TMSCl (272.0 mg, 2.504 mmol, 10 equiv) via syringe. The mixture was stirred at rt overnight, and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous phase was separated and extracted with

CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished using a 3 × 16 cm flash chromatography, eluting with 10% EtOAc/hexanes (500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (6-12) were combined and concentrated under reduced pressure to give the product **3.15** (191.5 mg, 84% over 3 steps) as a clear colorless oil: R_f = 0.28 (10% EtOAc/hexanes); $[\alpha]_D^{20}$ = -17.3 (*c* = 2.21, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.73-7.68 (m, 4H), 7.44-7.35 (m, 6H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.37 (dddd, *J* = 6.3, 6.3, 5.9, 5.9 Hz, 1H), 4.25-4.20 (m, 2H), 4.07 (d, *J* = 11.2 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 3.28 (dddd, *J* = 9.8, 5.4, 5.4, 5.4 Hz, 1H), 2.71 (dd, *J* = 14.6, 5.9 Hz, 1H), 2.62 (dd, *J* = 14.2, 5.9 Hz, 1H), 2.51 (dd, *J* = 15.1, 4.4 Hz, 1H), 2.43 (dd, *J* = 15.1, 8.3 Hz, 1H), 1.79 (ddd, *J* = 20.5, 7.8, 6.3 Hz, 1H), 1.65 (ddd, *J* = 13.7, 6.4, 6.4 Hz, 1H), 1.62-1.54 (m, 2H), 1.42 (s, 9H), 1.38-1.22 (m, 6H), 1.05 (s, 9H), 0.12 (s, 9H), 0.11 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) δ197.8, 172.2, 159.1, 136.1, 136.1, 134.1, 134.0, 131.1, 129.8, 129.8, 129.3, 127.8, 113.8, 76.1, 70.2, 69.6, 69.1, 67.2, 55.4, 53.0, 51.7, 48.1, 45.8, 43.0, 42.6, 37.8, 34.6, 30.0, 27.2, 21.4, 19.6, 0.7, 0.5; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 51.7, 30.0, 27.2, 0.7, 0.5; CH_2 δ 70.2, 53.0, 45.8, 43.0, 42.6, 37.8, 34.6, 21.4; CH δ 136.1, 136.1, 129.8, 129.8, 129.3, 127.8, 113.8, 76.1, 69.6, 69.1, 67.2; CH_0 δ 197.8, 172.2, 159.1, 134.1, 134.0, 131.1, 48.1, 19.6; IR (neat) 2954, 2859, 1741, 1682, 1613, 1513, 1430, 1364, 1301, 1250, 1168, 1108, 1038, 841, 744, 704, 610, 536 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{48}H_{76}NaO_8Si_3S$ (M+Na) 919.4466, found 919.4449.



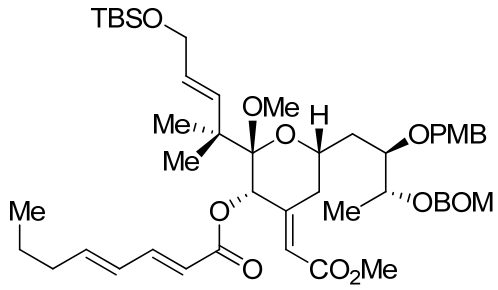
Preparation of (3*R*,5*S*,11*S*)-S-*tert*-butyl 3-((*tert*-butyldiphenylsilyl)oxy)-9,11-dihydroxy-5-((4-methoxybenzyl)oxy)-13-((trimethylsilyl)methyl)tetradec-13-enethioate (3.16). Powdered $CeCl_3 \cdot 7H_2O$ (1.451 g, 3.895 mmol, 10.0 equiv) was placed in a 25 mL rb flask and heated to 170 ºC under 1 mm Hg vacuum. After 16 h at 170 ºC, the dried $CeCl_3$ was cooled to rt, and the flask was purged with N_2. THF (5.0 mL) was added, and the mixture was stirred at rt for 2 h.

Meanwhile, a 25 mL three-necked rb flask equipped with condenser and magnetic stir bar was charged with magnesium turnings (124.0 mg, 5 mmol, 1.0 equiv), and a crystal of iodine. The flask was heated with a heat gun for 5 min while stirring. THF (5.0 mL) was added via syringe, and the reaction mixture was heated with the heat gun to reflux. $TMSCH_2Cl$ (0.613 g, 5.0 mmol, 1.0 equiv) was then added dropwise via syringe. The mixture was stirred at rt for 1.5 h to give an assumed 1.0 M solution of $TMSCH_2MgCl$.

The $CeCl_3$/THF mixture was cooled to -78 ºC, and then a solution of $TMSCH_2MgCl$ (3.895 mL of 1.0 M, 3.895 mmol, 10.0 equiv) was added to the mixture dropwise via syringe. After 1 h at -78 ºC, a solution of ester **3.15** (355.0 mg, 0.3895 mmol, 1.0 equiv) in THF (1.6 mL) was added to the reaction mixture via cannula. Additional THF (2 × 0.6 mL) rinse was used to transfer the remaining ester residue into the reaction mixture. The mixture was allowed to warm to rt and stirred overnight, and then cooled to -78 ºC, and quenched by the addition of saturated aqueous $NaHCO_3$ solution (5 mL). The mixture was then allowed to warm to rt and the phases were

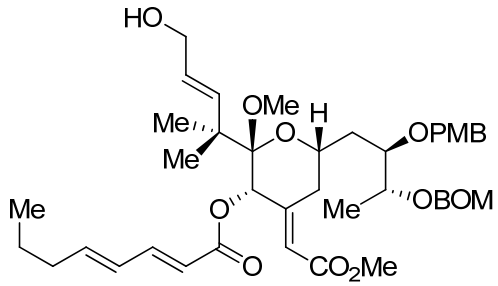
separated. The aqueous phase was extracted with Et_2O (3 × 30 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in THF (10 mL), and the resulting solution was cooled to 0 ºC. Two drops of 1N HCl solution was added into the flask via pipette. After 5 min at 0 ºC, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 mL). The reaction mixture was then allowed to warm to rt and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 3 × 14 cm column, eluting with 20% EtOAc/hexanes (1000 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (13-25) were combined and concentrated under reduced pressure to give the product **3.16** (159.1 mg, 51%) as a colorless oil: R_f = 0.59 (50% EtOAc/hexanes); $[\alpha]_D^{20}$ = -10.9 (*c* = 0.745, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.74-7.67 (m, 4H), 7.44-7.34 (m, 6H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 4.71 (s, 2H), 4.35 (dd, *J* = 6.4, 5.9 Hz, 1H),4.22 (d, *J* = 10.7 Hz, 1H), 4.08 (d, *J* =11.2, Hz, 1H), 3.98-3.92 (m, 1H), 3.80 (s, 3H), 3.79-3.74 (m, 1H), 3.30-3.22 (m, 2H), 2.78 (bs, 1H), 2.70 (dd, *J* = 14.7, 6.3 Hz, 1H), 2.63 (dd, *J* = 14.6, 5.9 Hz, 1H), 2.12 (d, *J* = 5.9 Hz, 2H), 1.79 (ddd, *J* = 14.2, 6.8, 6.8 Hz, 1H), 1.63-1.52 (m, 5H), 1.43 (s, 9H), 1.32-1.20 (m, 6H), 1.04 (s, 9H), 0.05 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) 198.1, 159.2, 144.2, 136.2, 136.1, 134.2, 134.0, 131.2, 129.9, 129.8, 129.4, 127.8, 127.8, 113.8, 110.8, 76.0, 72.6, 70.3, 70.1, 69.2, 55.5, 52.9, 48.1, 47.3, 42.5, 38.1, 34.1, 30.0, 27.2, 27.0, 20.9, 19.6, -1.2; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.5, 30.0, 27.2, -1.2; CH_2 δ 110.8, 70.1, 52.9, 47.3, 43.0, 42.5, 38.1, 34.1, 27.0, 20.9; CH δ 136.2, 136.1, 129.9, 129.8, 129.4, 127.8, 127.8, 113.8, 76.0,

72.6, 70.3, 69.2; CH_0 δ 198.1, 159.2, 144.2, 134.2, 134.0, 131.2, 48.1, 19.6; IR (neat) 3459 (broad), 3070, 2932, 2858, 1717, 1683, 1641, 1613, 1513, 1460, 1428, 1363, 1301, 1248, 1172, 1108, 1040, 850, 823, 739, 704, 610 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{46}H_{70}NaO_6Si_2S$ (M+Na) 829.4329, found 829.4319.



Preparation of (2*E*,4*E*)-((2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(4-methoxybenzyloxy) butyl)-2-((*E*)-5-(tert-butyldimethylsilyloxy)-2-methylpent-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2H-pyran-3-yl) octa-2,4-dienoate (3.18). This material was prepared from ketone **3.17** in the same manner as **2.105**. Purification was accomplished by flash chromatography on a 3 × 13 cm column, eluting with 10% EtOAc/hexanes (500 mL) and 15% EtOAc/hexanes (500 mL), collecting 18 × 150 mm test tube fractions. The product containing fractions (15-22) were combined and concentrated under reduced pressure to give the product **3.18** (86.7 mg, 87% over 2 steps) as a colorless oil: R_f = 0.54 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -9.4 (*c* = 0.34, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.39-7.34 (m, 4H), 7.33-7.27 (m, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.19-6.15 (m, 2H), 5.97 (d, *J* = 16.1 Hz, 1H), 5.91 (s, 1H), 5.75 (d, *J* = 15.1 Hz, 1H), 5.48 (s, 1H), 5.37 (ddd, *J* = 15.6, 5.4, 5.4 Hz, 1H), 4.87 (d, *J* = 2.4 Hz, 1H), 4.67 (d, *J* = 2.4 Hz, 1H), 4.62 (d, *J* = 10.7 Hz, 1H), 4.44 (d, *J* = 10.7 Hz, 1H), 4.12 (dd, *J* = 6.3, 4.9 Hz, 1H), 4.10-4.03 (m, 3H), 3.90 (ddd, *J* = 10.3, 4.4, 2.0

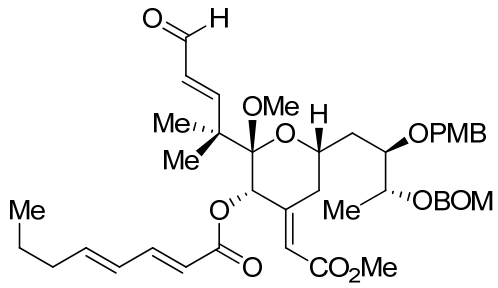
Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.52 (dd, *J* = 15.1, 2.0 Hz, 1H), 3.25 (s, 3H), 2.37-2.27 (m, 1H), 2.22-2.04 (m, 2H), 1.92 (ddd, *J* = 13.7, 9.5, 1.5 Hz, 1H), 1.74 (ddd, *J* = 14.2, 10.3, 2.4 Hz, 1H), 1.52-1.42 (m, 3H), 1.23 (d, *J* = 6.4 Hz, 3H), 1.13 (s, 3H), 1.12 (s, 3H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H) ; 125 MHz ^{13}C NMR ($CDCl_3$); 166.7, 165.6, 159.3, 152.7, 146.5, 145.7, 138.1,138.1, 130.7, 129.5, 128.7, 128.6, 128.0, 127.9, 125.0, 118.7, 117.5, 114.0, 102.9, 93.5, 77.0, 72.6, 72.1, 71.9, 69.6, 68.4, 64.8, 55.4, 51.7, 51.3, 45.9, 36.5, 35.3, 32.7, 26.2, 24.5, 23.7, 22.0, 18.6, 15.0, 13.9, -4.8; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 51.7, 51.3, 26.2, 24.5, 23.7, 15.0, 13.9, -4.8; CH_2 δ 93.5, 72.1, 69.6, 64.8, 36.5, 35.3, 32.7, 22.0; CH δ 146.5, 145.7, 138.1, 138.1, 129.5, 128.7, 128.6, 128.0, 127.9, 125.0, 118.7, 117.5, 114.0, 77.0, 72.6, 71.9, 68.4; CH_0 δ 166.7, 165.6, 159.3, 152.7, 130.7, 102,9, 45.9, 18.6; IR (neat) 2956, 2932, 1720, 1642, 1614, 1514, 1462, 1382, 1302, 1250, 1132, 1106, 1043, 836, 777, 737, 698, 590, 536 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{49}H_{72}NaO_{11}Si$ (M+Na) 887.4742, found 887.4734.



Preparation of (2*E*,4*E*)-((2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-2-((*E*)-5-hydroxy-2-methylpent-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2H-pyran-3-yl) octa-2,4-dienoate (3.19). To a stirring solution of the TBS ether **3.18** (36.8 mg, 0.0425 mmol, 1.0 equiv) in methanol (2.1 mL, 0.02 M) at 0 °C in a 25 mL rb flask was added CSA (2.0 mg, 0.0085 mmol, 0.2

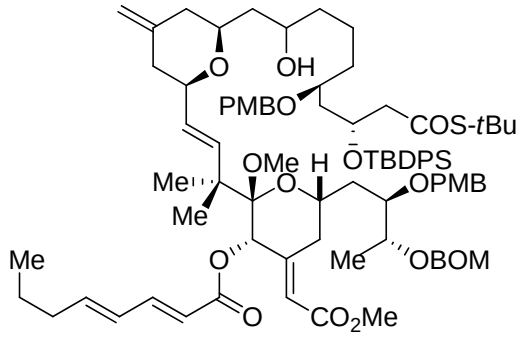
equiv). The solution was stirred at 0 °C for 3 h, and then quenched by pipetting it into a mixture of saturated aqueous $NaHCO_3$ solution (1 mL) and 50% EtOAc/hexanes (40 mL) in a separatory funnel. The aqueous phase was separated and extracted with 50% EtOAc/hexanes (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2 × 14 cm column, eluting with 30% EtOAc/hexanes (500 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (14-30) were combined and concentrated under reduced pressure to give the product **3.19** (31.2 mg, 98%) as a colorless oil: R_f = 0.18 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -20 (*c* = 0.20, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.40-7.34 (m, 4H), 7.33-7.28 (m, 1H), 7.22 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 7.8 Hz, 2H), 6.19 (s, 1H), 6.18 (d, *J* = 6.8 Hz, 1H), 5.99 (d, *J* = 16.1 Hz, 1H), 5.91 (s, 1H), 5.76 (d, *J* = 15.1 Hz, 1H), 5.51 (s, 1H), 5.47 (ddd, *J* = 15.1, 5.4, 5.4 Hz, 1H), 4.86 (d, *J* = 2.0 Hz, 2H), 4.68 (s, 2H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.43 (d, *J* = 10.7 Hz, 1H), 4.15 (dd, *J* = 6.5, 4.4 Hz, 1H), 4.10-4.04 (m, 1H), 4.01 (s, 2H), 3.92 (ddd, *J* = 9.8, 4.4, 2.0 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.49 (dd, *J* = 15.6, 2.4 Hz, 1H), 3.25 (s, 3H), 2.36 (t, *J* = 13.7 Hz, 1H), 2.23-2.14 (m, 2H), 1.95 (ddd, *J* = 14.2, 9.8, 2.0 Hz, 1H), 1.75 (ddd, *J* = 13.7, 10.3, 2.5 Hz, 1H), 1.52-1.41 (m, 3H), 1.23 (d, *J* = 6.4 Hz, 3H), 1.14 (s, 3H), 1.11 (s, 3H), 0.94 (t, *J* = 7.3 Hz, 3H) ; 125 MHz ^{13}C NMR ($CDCl_3$); 166.8, 165.8, 159.4, 152.6, 146.9, 146.2, 140.0, 138.1, 130.7, 129.5, 128.7, 128.5, 128.0, 128.0, 125.1, 118.6, 117.5, 114.0, 102.9, 93.5, 76.9, 72.5, 72.0, 72.0, 69.7, 68.6, 64.5, 55.5, 51.6, 51.3, 46.3, 36.4, 35.3, 32.9, 24.3, 22.1, 14.8, 13.9; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.5, 51.6, 51.3, 24.3, 14.8, 13.9; CH_2 δ 93.5, 72.0, 69.7, 64.5, 36.4, 35.3, 32.9, 22.1; CH δ 146.9, 146.2, 140.0, 129.5, 128.7, 128.5, 128.0, 128.0, 125.1, 118.6, 117.5, 114.0, 76.9, 72.5,

71.9, 68.6; CH_0 δ 166.8, 165.8, 159.4, 152.6, 138.1, 130.7, 102,9, 72.0; IR (neat); 3484 (b), 2932, 1717, 1642, 1614, 1513, 1459, 1382, 1302, 1249, 1134, 1106, 1041, 820, 739, 699, 590, 535 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{43}H_{58}NaO_{11}$ (M+Na) 773.3877, found 773.3871.



Preparation of (2*E*,4*E*)-((2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-(benzyloxymethoxy)-2-(4-methoxybenzyloxy)butyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-2-methyl-5-oxopent-3-en-2-yl)tetrahydro-2H-pyran-3-yl) octa-2,4-dienoate (3.5). This material was prepared from alcohol **3.19** in the same manner as **2.107**. Purification was accomplished by flash chromatography on a 2 × 12 cm column, eluting with 20% EtOAc/hexanes (500 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (12-24) were combined and concentrated under reduced pressure to give the product **3.5** (26.4 mg, 85%) as a colorless oil: R_f = 0.59 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -9 (*c* = 0.16, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.44 (d, *J* = 7.8 Hz, 1H), 7.37-7.23 (m, 5H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.22-7.16 (m, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 6.12-6.08 (m, 2H), 5.91 (dd, *J* = 16.1, 7.8 Hz, 1H), 5.90 (s, 1H), 5.60 (s, 1H), 5.58 (d, *J* = 15.6 Hz, 1H), 4.87 (t, *J* = 7.3 Hz, 1H), 4.85 (q, *J* = 7.8 Hz, 1H), 4.67 (s, 2H), 4.63 (d, *J* = 11.2 Hz, 1H), 4.42 (d, *J* = 10.7 Hz, 1H), 4.17 (dd, *J* = 6.4, 4.4 Hz, 1H), 4.16-.411 (m, 1H), 3.90 (ddd, *J* = 9.8, 3.9, 2.0 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.51 (dd, *J* = 16.1, 1.8 Hz,

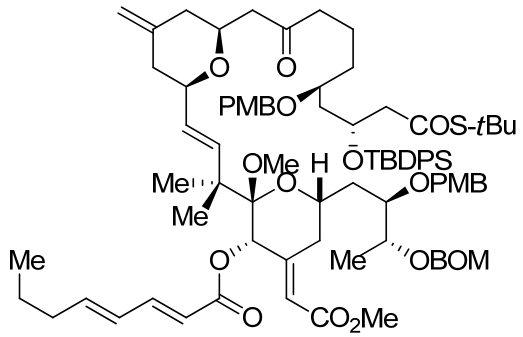
1H), 3.27 (s, 3H), 2.44 (dd, *J* = 14.7, 13.2 Hz, 1H), 2.16 (q, *J* = 6.8 Hz, 2H), 1.97 (ddd, *J* = 14.2, 9.8, 2.0 Hz, 1H), 1.78 (ddd, *J* = 13.7, 10.3, 2.5 Hz, 1H), 1.47 (q, *J* = 7.3 Hz, 2H), 1.27-1.20 (m, 1H), 1.24 (d, *J* = 6.4 Hz, 2H), 1.17 (s, 3H), 1.14 (s, 3H), 0.93 (t, *J* = 7.3 Hz, 3H) ; 125 MHz ^{13}C NMR ($CDCl_3$); 194.7, 166.8, 166.4, 165.2, 159.4, 152.1, 147.4, 146.6, 137.9, 130.5, 129.4, 128.6, 128.3, 127.9, 127.9, 127.2, 117.8, 117.4, 114.0, 102.8, 93.6, 76.7, 72.2, 71.8, 70.7, 69.7, 69.0, 55.5, 51.4, 47.6, 36.3, 35.3, 33.4, 23.7, 22.3, 22.0, 14.7, 13.9; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.5, 51.4, 23.7, 22.3, 14.7, 13.9; CH_2 δ 93.6, 71.8, 69.7, 36.3, 35.3, 33.4, 22.0; CH δ 194.7, 166.8, 147.4, 146.6, 129.4, 128.6, 128.3, 127.9, 127.9, 127.2, 117.8, 117.4, 114.0, 76.7, 72.2, 70.7, 69.0,; CH_0 δ 166.4, 165.2, 159.4, 152.1, 137.9, 130.5, 102.8, 47.6; IR (neat); 3484 (b), 2956, 1718, 1687, 1641, 1513. 1459, 1381, 1302, 1248, 1133, 1042, 819, 739, 699, 589, 535 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{43}H_{56}NaO_{11}$ (M+Na) 771.3720, found 771.3734.



Preparation of (2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((4-methoxybenzyl)oxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-((6*S*,8*R*)-8-((*tert*-butyldiphenylsilyl)oxy)-10-(*tert*-butylthio)-2-hydroxy-6-((4-methoxybenzyl)oxy)-10-oxodecyl)-4-methylenetetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene) tetrahydro-2H-pyran-3-yl octa-2,4-dienoate (3.20). To a stirring

solution of hydroxyallylsilane **3.16** (8.1 mg, 0.0010 mmol, 1.1 equiv) and aldehyde **3.5** (7.1 mg, 0.0095 mmol, 1.0 equiv) in Et_2O (1.0 mL, 0.01M) in a 10 mL rb flask at -78 ºC was added a solution of TMSOTf in Et_2O (34.2 μL of 1.0 M, 0.0342 mmol, 3.6 equiv) via syringe. After 1 h at -78 ºC, the reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 mL). The mixture was warmed to rt, and then the aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2 × 15 cm column, eluting with 20% EtOAc/hexanes (500 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (28-37) were combined and concentrated under reduced pressure to give the product **3.20** (7.1 mg, 51% yield) as colorless oil: R_f = 0.45 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -15 (*c* = 0.13, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.66 (m, 4H), 7.42-7.30 (m, 13H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.85-6.79 (m, 4H), 6.20-6.16 (m, 2H), 6.04 (d, *J* = 16.1 Hz, 1H), 5.90 (s, 1H), 5.77 (d, *J* = 15.6 Hz, 1H), 5.52 (s, 1H), 5.35 (dd, *J* = 16.1, 6.4 Hz, 1H), 4.86 (s, 2H), 4.73 (d, *J* = 14.2 Hz, 2H), 4.67 (d, *J* = 4.9 Hz, 2H), 4.62 (d, *J* = 10.7 Hz, 1H), 4.44 (d, *J* = 10.7 Hz, 1H), 4.34 (t, *J* = 5.7 Hz, 1H), 4.21 (d, *J* =10.7 Hz, 1H), 4.14-4.08 (m, 2H), 4.05 (d, *J* = 10.7 Hz, 1H), 3.92-3.86 (m, 1H), 3.80-3.70 (m, 4H), 3.79 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 3.54-3.46 (m, 2H), 3.24 (s, 3H), 2.67 (dd, *J* = 15.6, 6.3 Hz, 1H), 2.61 (dd, *J* = 14.2, 5.9 Hz, 1H), 2.22-2.12 (m, 4H), 2.04-1.88 (m, 4H), 1.79-1.70 (m, 2H), 1.65-1.45 (m, 9H), 1.41 (s, 9H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 1.02 (s, 9H), 0.92 (t, *J* = 7.3 Hz, 3H) ; 125 MHz ^{13}C NMR ($CDCl_3$); 198.0, 166.7, 165.6, 159.3, 159.1, 152.8, 146.7, 146.0, 143.7, 139.7, 138.1, 136.1, 134.2, 130.7, 129.9, 129.8, 129.5, 129.4, 128.7, 128.6, 128.0, 127.9,

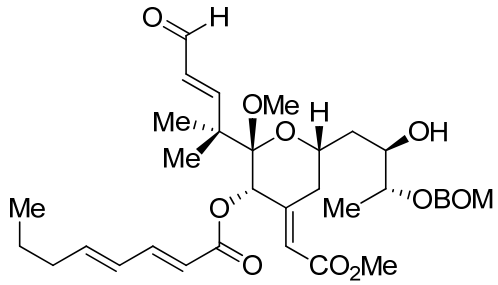
127.8, 125.8, 118.6, 117.4, 114.0, 113.8, 109.4, 93.6, 79.9, 79.4, 77.1, 76.0, 72.8, 72.2, 71.9, 70.1, 69.7, 69.1, 68.4, 55.5 (×2), 52.9, 51.7, 51.3, 48.1, 46.1, 42.6, 42.5, 41.1, 40.6, 37.8, 36.6, 35.3, 34.3, 32.9, 30.0, 27.2, 24.5, 23.8, 22.1, 21.0, 19.6, 15.1, 14.0; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.5 (×2), 51.7, 51.4, 30.0, 27.2, 24.5, 23.9, 15.1, 14.0; CH_2 δ 109.4, 93.6, 72.2, 70.1, 69.7, 52.9, 42.6, 42.5, 41.1, 40.6, 37.8, 36.6, 35.3, 34.3, 32.9, 22.1, 21.0; CH δ 146.7, 146.0, 139.7, 136.1, 129.9, 129.8, 129.5, 129.4, 128.7, 128.6, 128.0,127.9, 127.8, 125.8, 118.6, 117.4, 114.0, 113.8, 79.9, 79.4, 77.1, 76.0, 72.8, 69.1, 68.4; CH_0 δ 198.0, 166.7, 165.6, 159.3, 159.1, 152.8, 143.7, 138.1,136.2, 134.2, 134.0,131.2,130.7, 48.1, 46.1, 19.6; IR (neat); 3512, 2953, 1718, 1686, 1642, 1613, 1513, 1460, 1362, 1302, 1248, 1107, 1042, 888, 831, 740 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{86}H_{116}NaO_{16}$ (M+Na) 1487.7651, found 1487.7662.



Preparation of (2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-((4-methoxybenzyl)oxy)butyl)-2-((*E*)-4-((2*R*,6*S*)-6-((6*S*,8*R*)-8-((*tert*-butyldiphenylsilyl) oxy)-10-(*tert*-butylthio)-6-((4-methoxybenzyl)oxy)-2,10-dioxodecyl)-4-methylene tetrahydro-2H-pyran-2-yl)-2-methylbut-3-en-2-yl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)tetrahydro-2H-pyran-3-yl octa-2,4-dienoate (3.21) To a stirring solution of alcohol **3.20** in MeCN (0.778 mL, 0.005 M) was added TEMPO (18.2 mg, 0.117 mmol,

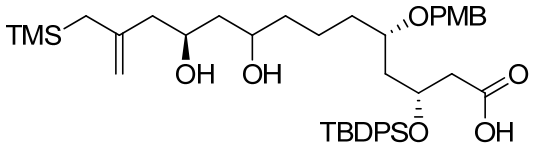
30 equiv) and diacetate iodobenene (37.7 mg, 0.117 mmol, 30 equiv). The reaction mixture was stirred at rt for 2 h, and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (1 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was accomplished by flash chromatography on a 2 × 13 cm column, eluting with 20% EtOAc/hexanes (500 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (10-25) were combined and concentrated under reduced pressure to give the product **3.21** (4.7 mg, 83%) as colorless oil: R_f = 0.45 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -18 (*c* = 0.08, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.66 (m, 4H), 7.42-7.30 (m, 13H), 7.21 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.85-6.79 (m, 4H), 6.20-6.16 (m, 2H), 6.01 (d, *J* = 16.1 Hz, 1H), 5.90 (s, 1H), 5.77 (d, *J* = 15.6 Hz, 1H), 5.52 (s, 1H), 5.35 (dd, *J* = 16.1, 6.0 Hz, 1H), 4.86 (ABq, J = 7.3, Δν = 5.7 Hz, 2H), 4.73 (d, *J* = 14.2 Hz, 2H), 4.67 (d, *J* = 4.9 Hz, 2H), 4.62 (d, *J* = 10.7 Hz, 1H), 4.43 (d, *J* = 10.7 Hz, 1H), 4.34 (t, *J* = 5.7 Hz, 1H), 4.21 (d, *J* =10.7 Hz, 1H), 4.14-4.08 (m, 2H), 4.04 (d, *J* = 10.7 Hz, 1H), 3.92-3.86 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.74-3.68 (m, 3H), 3.66 (s, 3H), 3.3.47 (d, *J* = 4.7 Hz, 1H), 3.23 (s, 3H), 2.68 (dt, *J* = 15.1, 5.9 Hz, 2H), 2.61 (dd, *J* = 14.2, 5.9 Hz, 1H), 2.40 (dd, *J* = 16.1, 6.4 Hz, 2H), 2.25 (dd, *J* = 7.8, 4.4 Hz, 2H), 2.20-2.12 (m, 3H), 2.00-1.84 (m, 3H), 1.84-1.70 (m, 3H), 1.59-1.44 (m, 5H), 1.42 (s, 9H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.12 (s, 3H), 1.10 (s, 3H), 1.02 (s, 9H), 0.94 (t, *J* = 7.3 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$); 208.6, 198.0, 166.7, 165.7, 159.4, 159.1, 153.0, 146.8, 146.0, 143.8, 138.9, 138.1, 136.2, 126.1, 134.1, 134.0, 131.1, 130.7, 129.9, 129.9, 129.5, 129.4, 128.7, 128.6, 128.0, 127.9, 127.8, 126.4, 118.6, 117.0, 114.0, 113.8, 109.5, 102.8, 93.6, 79.3, 75.7, 74.5, 72.6, 72.1, 71.6, 70.1, 69.7, 69.1,

68.3, 55.5, 52.9, 51.5, 51.3, 49.2, 48.2, 46.2, 44.0, 42.4, 40.6, 40.5, 36.4, 35.2, 33.4, 29.9, 27.1, 24.2, 24.0, 22.0, 19.1, 14.9, 13.9; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.5 51.4, 51.3, 30.0, 27.1, 24.3, 24.0, 14.9, 13.9; CH_2 δ 109.5, 93.6, 72.1, 70.1, 69.7, 52.9, 49.2, 43.9, 42.4, 40.6, 40.5, 36.4, 35.3, 33.5, 33.2, 22.1, 19.1; CH δ 146.8, 146.1, 138.9, 136.1, 129.9, 129.9, 129.5, 129.4, 128.7, 128.6, 128.0, 127.9, 127.8, 126.3, 118.6, 117.0, 114.0, 113.8, 79.3, 75.7, 74.5, 72.6, 71.6, 69.0, 68.3; CH_0 δ 208.6, 198.0, 166.7, 165.7, 159.4, 159.1, 153.0, 143.8, 138.1, 134.1, 134.0, 131.1, 130.7, 48.2, 46.2, 19.1; IR (neat); 2929, 1717, 1681, 1642, 1613, 1513, 1460, 1363, 1302, 1247, 1107, 1042, 821, 738 cm^{-1}.



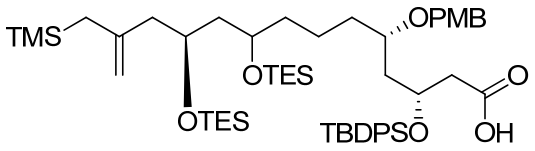
Preparation of (2*E*,4*E*)-(2*S*,3*S*,6*S*,*E*)-6-((2*R*,3*R*)-3-((benzyloxy)methoxy)-2-hydroxybutyl)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-((*E*)-2-methyl-5-oxopent-3-en-2-yl)tetrahydro-2H-pyran-3-yl octa-2,4-dienoate (3.28) To a stirring solution of PMB ether **3.5** (13.4 mg, 0.0179 mmol, 1.0 equiv) in CH_2Cl_2 (1.2 mL, 0.015 M) in a 10 mL rb flask at 0 ºC was added *tert*-butyl alcohol (0.6 mL) and aqueous pH 7 buffer (0.6 mL) and DDQ (40.6 mg, 0.179 mmol, 10.0 equiv). The reaction mixture was stirred at 0 ºC for 5 h, and then quenched by the addition of saturated aqueous $NaHCO_3$ solution (2 mL). After being stirred vigorously for 10 min at rt, the aqueous phase was separated and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was

accomplished by flash chromatography on a 2 × 13 cm column, eluting with 30% EtOAc/hexanes (500 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (19-35) were combined and concentrated under reduced pressure to give the product **3.28** (8.0 mg, 83%) as colorless oil: R_f = 0.29 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -20 (*c* = 0.18, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.48 (d, *J* = 7.8 Hz,1H), 7.38 -7.30 (m, 5H), 7.19 (dd, *J* = 15.1, 9.8 Hz, 1H), 6.16-6.11 (m, 2H), 5.92 (dd, *J* = 16.1, 7.8 Hz, 1H), 5.90 (s, 1H), 5.64 (s, 1H), 5.58 (d, *J* = 15.6 Hz, 1H), 4.86 (d, *J* = 6.8 Hz, 1H), 4.68 (ABq, *J* = 11.7 Hz, Δν = 17.5 Hz, 2H), 4.35-4.28 (m, 1H), 3.90-3.83 (m 1H), 3.70 (s, 3H), 3.70-3.67 (m, 1H), 3.65 (t, *J* = 6.4 Hz, 1H), 3.50-3.45 (m, 1H), 3.46 (s, 3H), 2.71 (d, *J* = 4.4 Hz, 1H), 2.46 (dd, *J* = 14.2, 13.7 Hz, 1H), 2.16 (dd, *J* = 13.2, 6.8 Hz, 2H), 1.77-1.72 (m, 2H), 1.47 (ddddd, *J* = 7.3, 7.3, 7.3, 7.3, 7.3 Hz, 2H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.20 (s, 3H), 1.16 (s, 3H), 0.93 (t, *J* = 7.3 Hz, 3H); 125 MHz ^{13}C NMR ($CDCl_3$) 195.0, 167.1, 166.6, 165.3, 152.4, 147.6, 146.7, 137.6, 128.8, 128.4, 128.1, 128.1, 127.1, 117.8, 117.2, 102.8, 94.0, 78.3; 125 MHz DEPT ($CDCl_3$) CH_3 δ 51.4, 51.4, 23.7, 22.4, 17.1, 13.9; CH_2 δ 94.0, 70.2, 39.9, 35.3, 33.4, 22.0; CH δ 195.0, 167.1, 147.6, 146.7, 128.8, 128.4, 128.1, 128.1, 127.1, 117.8, 117.2, 78.3, 71.2, 70.8, 68.5; CH_0 δ 166.6, 165.3, 152.4, 137.6, 102.8, 47.6; IR (neat); 3507, 2952, 2929, 2875, 2724, 1716, 1685, 1496, 1455, 1433, 1241, 1214, 1176, 1103, 1040, 1004, 857, 783, 742 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{35}H_{48}NaO_{10}$ (M+Na) 651.3145, found 651.3143.



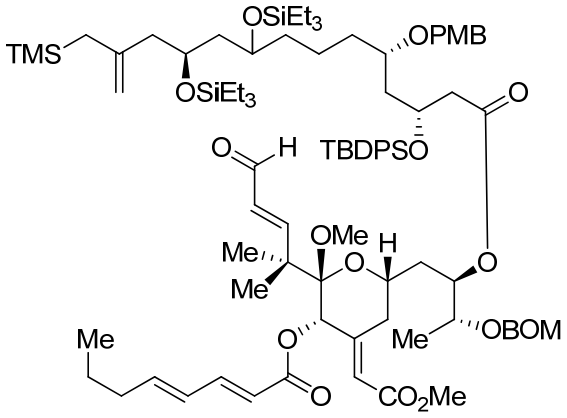
Preparation of (3*R*,5*S*,11*S*)-3-(*tert*-butyldiphenylsilyloxy)-9,11-dihydroxy-5-(4-methoxybenzyloxy)-13-((trimethylsilyl)methyl)tetradec-13-enoic acid (3.29). To a stirring solution of thiolester **3.16** (36.7 mg, 0.0455 mmol, 1.0 equiv) in a mixture of 4:1 THF/H_2O (4.6 mL, 0.01 M) in a 25 mL rb flask at 0 ºC was added LiOH•H_2O (19.1 mg, 0.455 mmol, 10 equiv) and H_2O_2 (103 μL, 0.910 mmol, 20 equiv). The mixture was stirred at 0 °C for 1 h, and then warmed to rt and stirred overnight. The mixture was diluted with 50% EtOAc/hexanes (20 mL), quenched by the addition of pH 4 buffer solution (5 mL). The aqueous phase was separated and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. Purification was accomplished by flash chromatography on a 2 × 16 cm column, eluting with 5% MeOH/15% EtOAc/hexanes (500 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (10-12) were combined and concentrated under reduced pressure to give the product **3.29** (28.5 mg, 85%) as a colorless oil: R_f = 0.31 (5% MeOH/30% EtOAc/hexanes), $[\alpha]_D^{20}$ = +1 (*c* = 0.14, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.65 (m, 4H), 7.45-7.30 (m, 6H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H), 4.70 (s, 2H), 4.30-4.20 (m, 2H), 4.05 (d, *J* = 10.7 Hz, 1H), 3.92-3.82 (m, 1H), 3.81-3.77 (m, 2H), 3.78 (s, 3H), 3.29-3.24 (m, 1H), 2.57 (dd, *J* = 15.1, 5.9 Hz, 1H), 2.53 (dd, *J* = 15.1, 5.4 Hz, 1H), 2.16-2.06 (m, 2H), 1.88-1.78 (m, 1H), 1.68 (dt, *J* = 14.2, 5.4 Hz, 1H), 1.60-1.48 (m, 5H), 1.48-1.28 (m, 7H), 1.04 (s, 9H), 0.04 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) 175.1, 159.2, 144.1, 136.1, 136.1, 135.2, 133.8, 133.6, 130.7, 130.0, 129.5, 127.9, 114.0, 110.8, 75.9, 72.5, 70.2, 68.9, 66.4, 55.4, 47.3, 42.9, 42.7, 37.9, 33.8, 27.1, 26.9, 20.7, 19.5, -1.2; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 27.1, -1.2; CH_2 δ 110.8, 70.2, 47.3, 42.9, 42.7, 42.2, 37.9, 33.8, 26.9,

20.7; CH δ 136.1, 136.1, 130.0, 129.6, 129.5, 127.9, 113.9, 75.9, 72.5, 70.2, 68.9; CH_0 δ 175.1, 159.2, 144.1, 135.2, 133.8, 19.5; IR (neat); 3379, 3071, 2932, 2857, 1712, 1612, 1561, 1248, 1172, 1110, 847, 822, 704 cm^{-1}.



Preparation of (3*R*,5*S*,11*S*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-((4-methoxybenzyl)oxy)-9,11-bis((triethylsilyl)oxy)-13-((trimethylsilyl)methyl)tetradec-13-enoic acid (3.30). To a stirring solution of alcohol **3.29** (8.8 mg, 0.012 mmol, 1.0 equiv) in CH_2Cl_2 (0.6 mL, 0.02 M) at 0 °C was added imidazole (8.2 mg, 0.12 mmol, 10 equiv) and TESCl (9.0 mg, 0.060 mmol, 5 equiv) via syringe. The mixture was stirred at 0 °C for 1 h, and then diluted with CH_2Cl_2 (5 mL), and quenched by the addition of saturated aqueous NH_4Cl solution (5 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. Purification was accomplished by flash chromatography on a 2 × 15 cm column, eluting with 20% EtOAc/hexanes (500 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (9-20) were combined and concentrated under reduced pressure to give the product **3.30** (8.6 mg, 75%) as a colorless oil: R_f = 0.23 (20% EtOAc/hexanes), $[\alpha]_D^{20}$ = +7.6 (*c* = 0.18, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 7.72-7.65 (m, 4H), 7.45-7.30 (m, 6H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.82 (d, *J* = 8.3 Hz, 2H), 4.65-4.58 (m, 2H), 4.30-4.25 (m, 2H), 4.01 (d, *J* = 10.7 Hz, 1H), 3.91-3.86 (m, 1H), 3.81-3.77 (m, 1H), 3.79 (s, 3H), 3.28-3.20 (m, 1H), 2.58 (dd, *J* = 9.8, 5.4 Hz, 1H), 2.50 (dd, *J* = 15.1, 5.4 Hz, 1H), 2.20 (ddd, *J* =32.7, 13.7, 5.3 Hz, 1H), 2.07

(ddd, *J* = 15.615.6, 7.8 Hz, 1H), 1.86-1.78 (m, 1H), 1.72-1.62 (m, 2H), 1.60-1.48 (m, 3H), 1.46-1.15 (m, 6H), 1.05 (s, 9H), 0.98 (t, *J* = 8.3 Hz, 9H), 0.97 (t, *J* = 8.3 Hz, 9H), 0.61 (q, *J* = 7.8 Hz, 6H), 0.60 (q, *J* = 7.8 Hz, 6H), 0.04 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) 176.4, 159.2, 144.3, 136.2, 136.1, 133.8, 133.8, 130.9, 130.0, 129.4, 127.9, 127.8, 113.9, 110.2, 110.2, 76.3, 70.2, 69.7, 69.3, 69.0, 68.9, 55.4, 47.4, 47.0, 45.5, 45.2, 42.9, 42.6, 38.6, 37.5, 34.7, 34.5, 29.9, 27.5, 27.3, 27.1, 27.1, 20.9, 19.5, 7.3, 7.2, 5.6, 5.4, -1.2; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 27.1, 7.2, 7.2, -1.2; CH_2 δ 110.1, 70.2, 47.3, 42.9, 42.7, 42.2, 37.9, 33.8, 26.9, 21.0, 5.6, 5.3; CH δ 136.1, 136.1, 130.0, 129.6, 129.5, 127.9, 113.9, 75.9, 72.5, 70.2, 68.9; CH_0 δ 175.1, 159.2, 144.1, 135.2, 133.8, 19.5; IR (neat) 2932, 2867, 1712, 1611,1563, 1248, 1172, 1110, 847, 822, 704 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{54}H_{90}NaO_7$ (M+Na) 985.5661, found 985.5680.



Preparation of (3*R*,5*S*,11*S*)-(2*R*,3*R*)-3-((benzyloxy)methoxy)-1-((2*S*,5*S*,6*S*,*E*)-6-methoxy-4-(2-methoxy-2-oxoethylidene)-6-((*E*)-2-methyl-5-oxopent-3-en-2-yl)-5-((2*E*,4*E*)-octa-2,4-dienoyloxy) tetrahydro-2H-pyran-2-yl)butan-2-yl 3-((tert-butyldi phenylsilyl)oxy)-5-((4-methoxybenzyl) oxy)-9,11-bis((triethylsilyl)oxy)-13-((trimethyl silyl) methyl) tetradec-13-enoate (3.31). To a stirring solution of carboxylic acid **3.30**

(9.1 mg, 0.0094 mmol, 1.1 equiv) in toluene (0.86 mL) at rt was added triethylamine (4.4 mg, 0.043 mmol, 5.0 equiv) and 2,4,6-trichlorobenzoyl chloride (2.5 mg, 0.010 mmol, 1.2 equiv). The mixture was stirred at rt for 3 h. A solution of alcohol **3.28** (5.4 mg, 0.0086 mmol, 1.0 equiv) in toluene (0.4 mL) was added via syringe. The residue of alcohol was rinsed with toluene (2×0.2 mL) and the solutions were transferred to the reaction flask via syringe. DMAP (2.8 mg, 0.023 mmol, 2.7 equiv) was added in one portion. The mixture was stirred at rt for 0.5 h. Purification was accomplished by flash chromatography on a 2 × 12 cm column, eluting with 15% EtOAc/hexanes (500 mL), collecting 13 × 100 mm test tube fractions. The product containing fractions (8-13) were combined and concentrated under reduced pressure to give the product **3.31** (11.3 mg, 84%) as a colorless oil: R_f = 0.61 (30% EtOAc/hexanes); $[\alpha]_D^{20}$ = -6 (*c* = 0.16, $CHCl_3$); 500 MHz ^{1}H NMR ($CDCl_3$) δ 9.44 (d, *J* = 7.3 Hz, 1H), 7.70-7.66 (m, 2H), 7.45-7.32 (m, 8H), 7.30-7.20 (m, 5H), 7.17 (dd, *J* = 15.6, 9.8 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.18-6.10 (m, 2H), 5.93 (s, 1H), 5.85 (dd, *J* = 16.1, 7.8 Hz, 1H), 5.54 (d, *J* = 15.1 Hz, 1H), 5.44 (s, 1H), 5.31-5.26 (m, 1H), 4.75 (s, 2H), 4.68-4.57 (m, 2H), 4.61 (s, 2H), 4.41-4.35 (m, 1H), 4.31 (d, *J* = 10.8 Hz, 1H), 4.01 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.19-3.82 (m, 2H), 3.79 (s, 3H), 3.82-3.68 (m, 4H), 3.70 (s, 3H), 3.54 (d, *J* = 15.6 Hz, 1H), 3.51-3.44 (m, 1H), 3.11 (s, 3H), 2.47 (dd, *J* = 15.1, 5.4 Hz, 1H), 2.40 (dd, *J* = 15.1, 7.8 Hz, 1H), 2.31 (dd, *J* = 13.7, 13.2 Hz, 1H), 2.16 (ABq, *J* = 6.8 Hz, Δν = 12.2 Hz, 2H), 2.10-2.04 (m,1H), 1.93 (td, *J* = 12.2, 2.4 Hz, 1H), 1.80-1.74 (m, 1H), 1.72-1.64 (m, 2H), 1.60-1.52 (m, 3H), 1.50-1.40 (m, 5H), 1.38-1.22 (m, 5H), 1.12 (s, 3H), 1.09 (s, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 1.02 (s, 9H), 1.00-0.94 (m, 18H), 0.60 (q, *J* = 7.8 Hz, 12 H), 0.03 (s, 9H); 125 MHz ^{13}C NMR ($CDCl_3$) 195.0, 170.5, 166.8, 166.6, 165.2, 159.1, 151.5, 147.5,

146.7, 144.3, 137.9, 136.1, 134.0, 133.8, 131.3, 130.0, 129.2, 128.7, 128.3, 128.0, 127.9, 127.8, 126.9, 118.1, 117.8, 113.7,110.2, 93.7, 76.1, 73.0, 71.1, 70.3, 70.1, 69.8, 69.3, 69.0, 68.4, 68.1, 55.5, 51.4, 51.3, 47.3, 47.0, 45.5, 45.3, 43.6, 43.0, 38.7, 37.6, 35.3, 34.8, 32.5, 31.8, 27.1, 23.8, 22.1, 21.2, 19.5, 15.4, 13.9, 7.3, 7.2, 5.7, 5.4, -1.2; 125 MHz DEPT ($CDCl_3$) CH_3 δ 55.4, 51.4, 51.3, 27.0, 23.8, 22.0, 15.3, 13.9, 7.3, 7.2, -1.2; CH_2 δ 110.1, 93.6, 70.1, 69.7, 47.3, 47.0, 45.2, 43.5, 43.0, 38.6, 37.6, 35.5, 35.3, 32.4, 22.0, 21.2, 5.7, 5.4; CH δ 195.0, 166.7, 147.5, 146.7, 136.1, 129.9, 129.2, 128.6, 128.3, 128.0, 127.9, 127.8, 126.9, 118.1, 117.8, 113.7, 76.0, 73.0, 71.1, 70.3, 69.3, 68.9, 68.4, 68.1; CH_0 δ 170.5, 166.8, 165.2, 159.1, 151.5, 144.3, 137.9, 134.0, 133.9, 131.3, 45.5, 19.5; IR (neat) 2952, 2911, 2876, 1720, 1688, 1246, 1106, 1042, 1005, 854, 740, 481 cm^{-1}; HRMS (ESI/TOF) calcd for $C_{89}H_{136}NaO_{16}$ (M+Na) 1595.8803, found 1595.8798.

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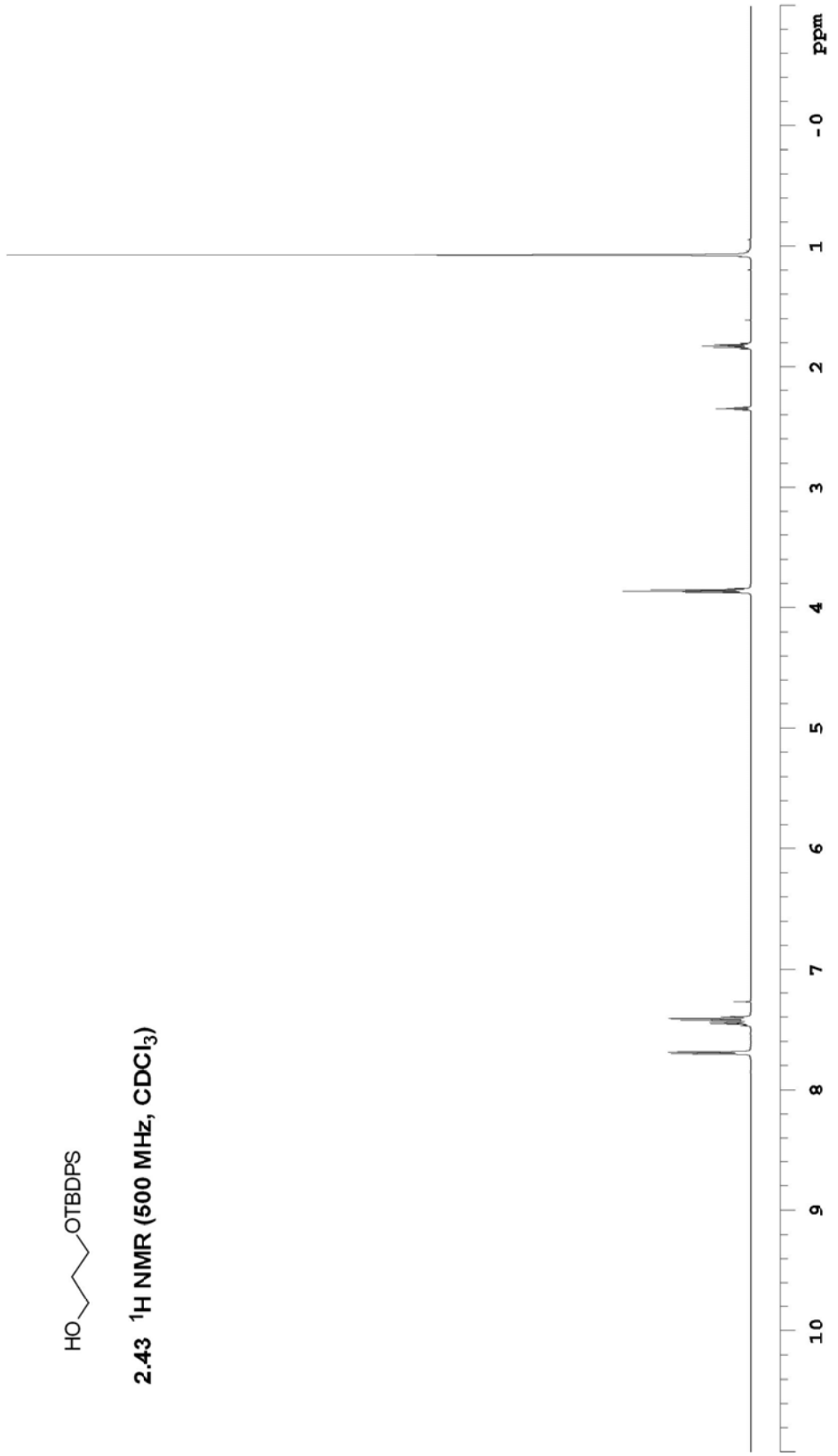
APPENDIX A

NMR SPECTRA OF CHAPTER 2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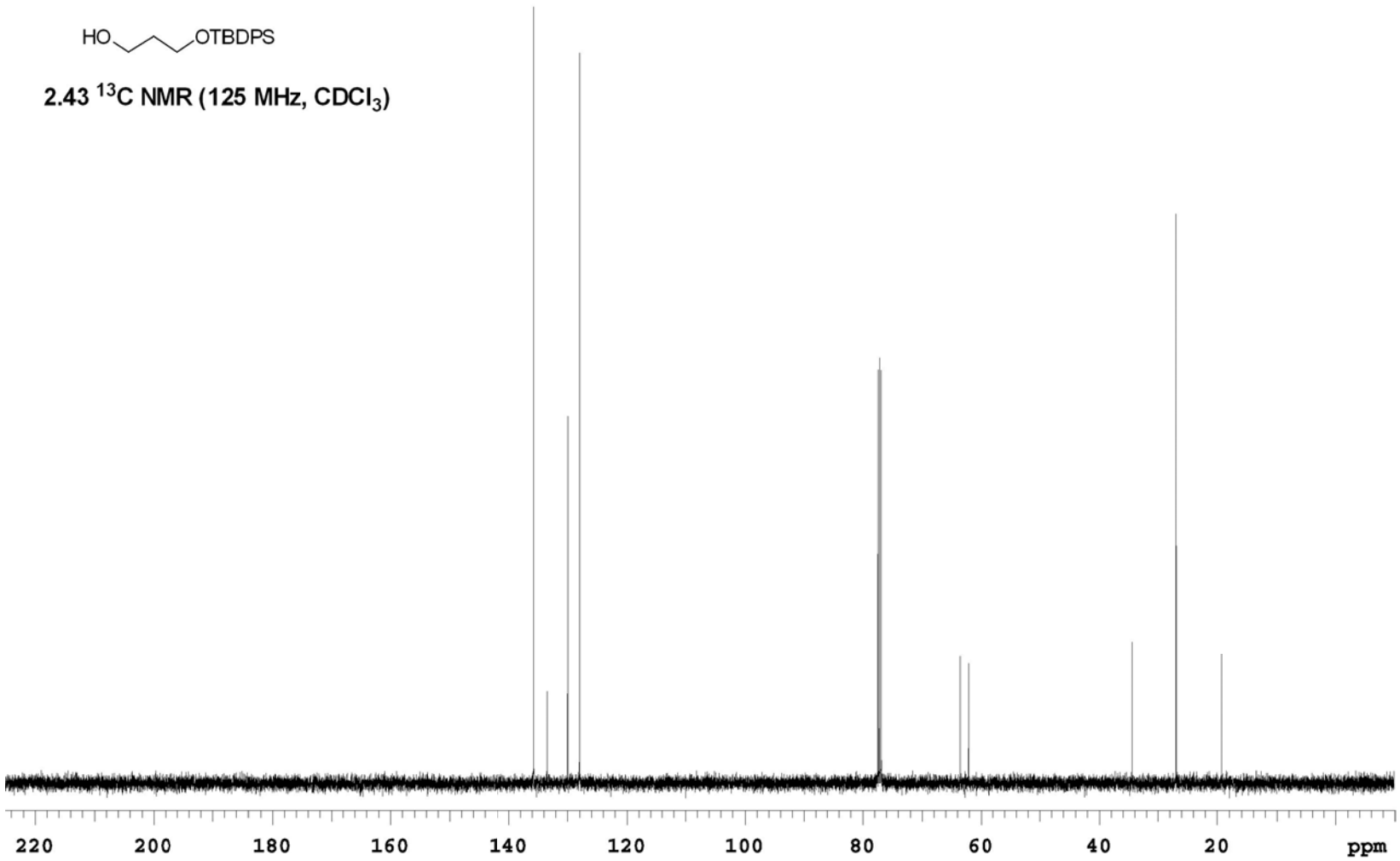
10
9
8
7
6
5
4
3
2
1
-0
ppm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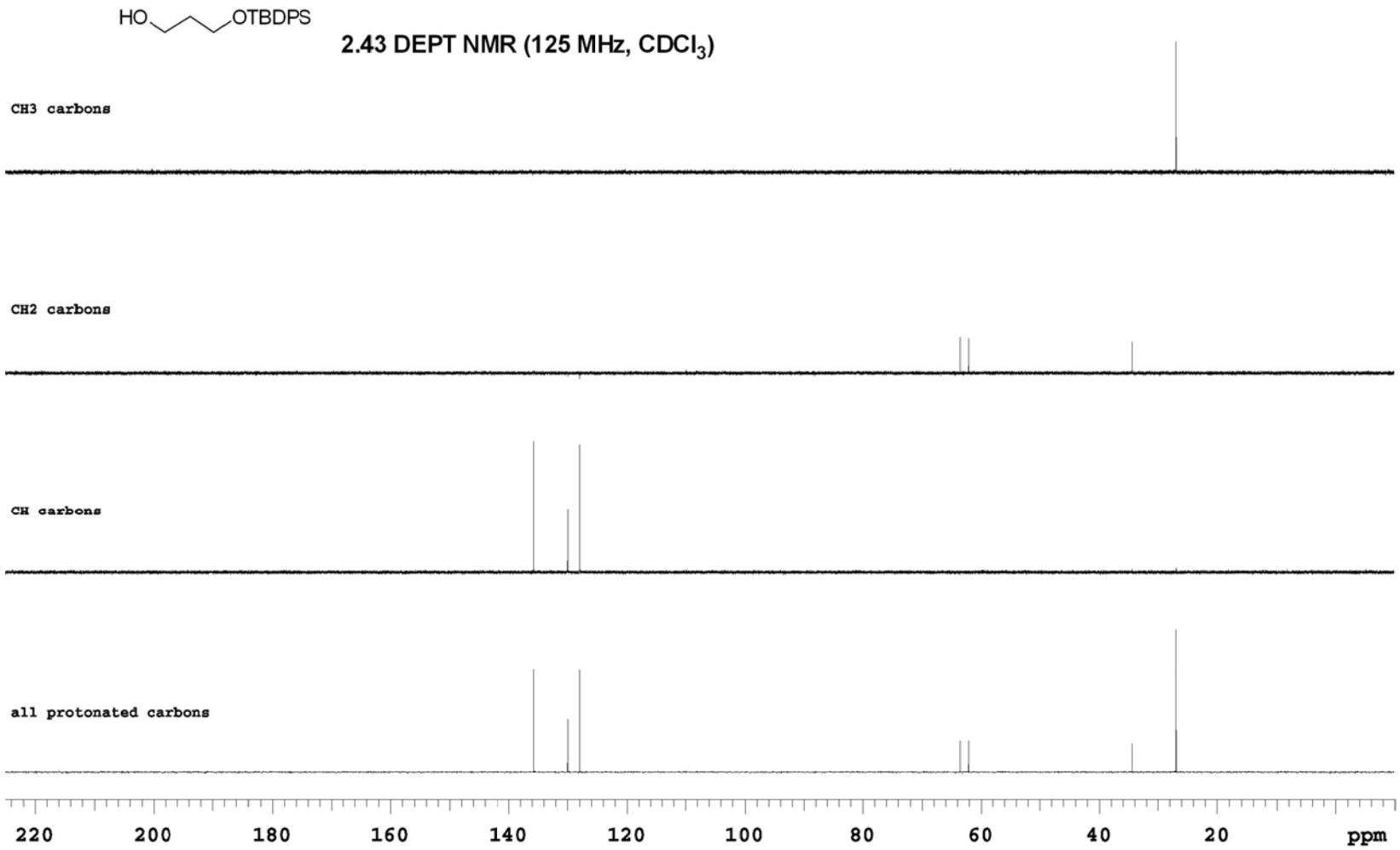
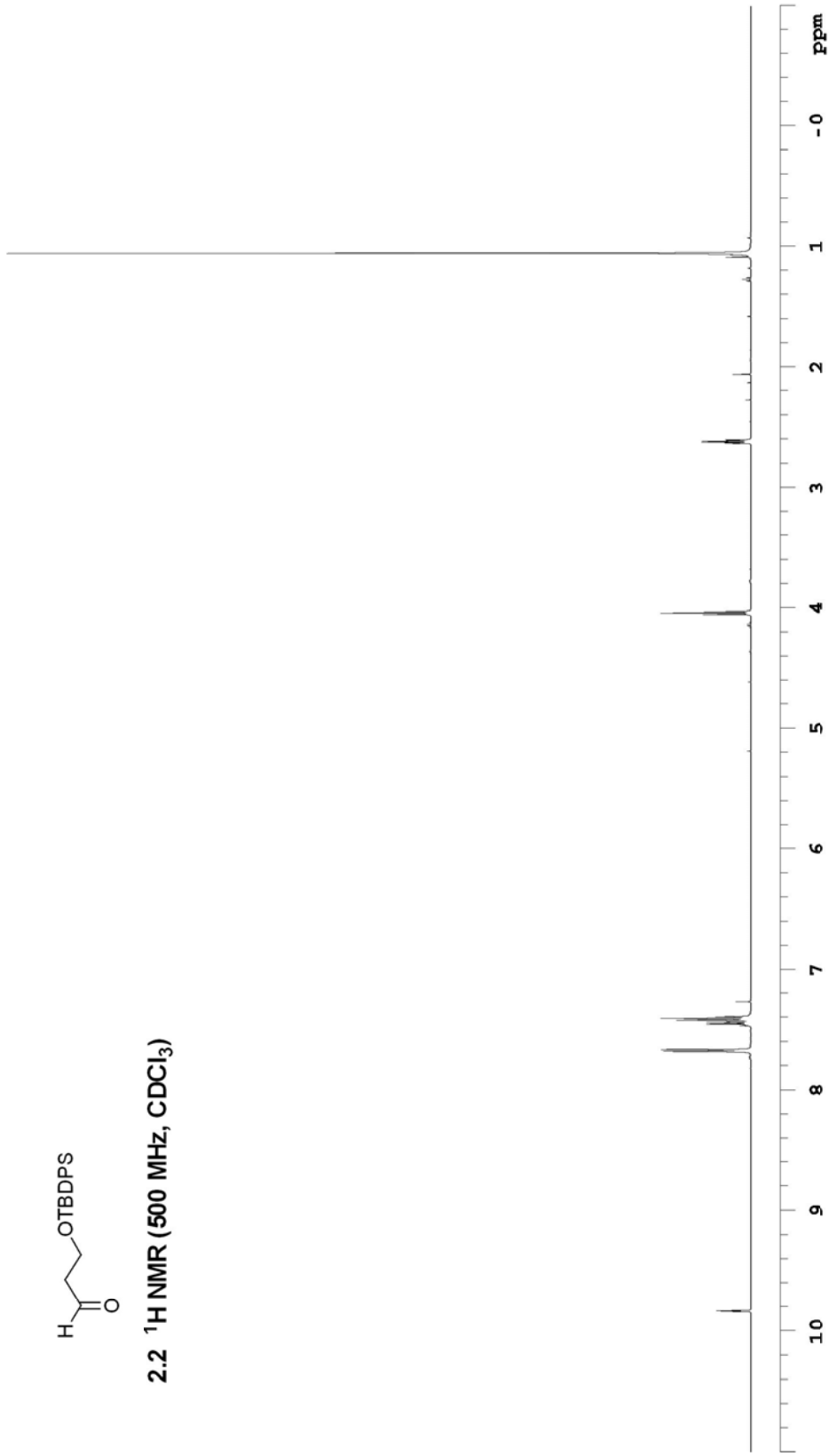
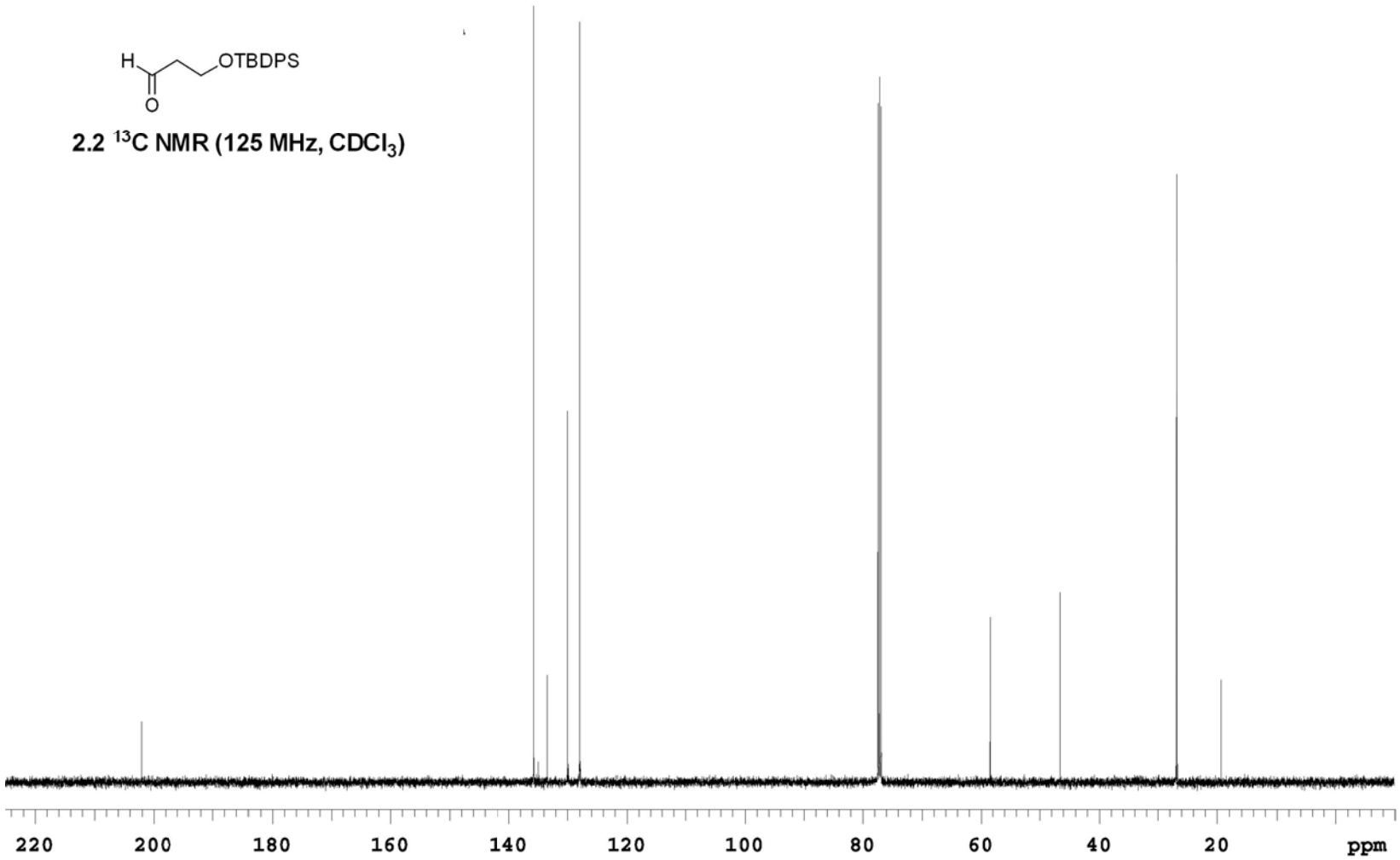
220
200
180
160
140
120
100
80
60
40
20
ppm


HO
OTBDPS
2.43 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
ppm



2.2 ^{1}H NMR (500 MHz, $CDCl_3$)



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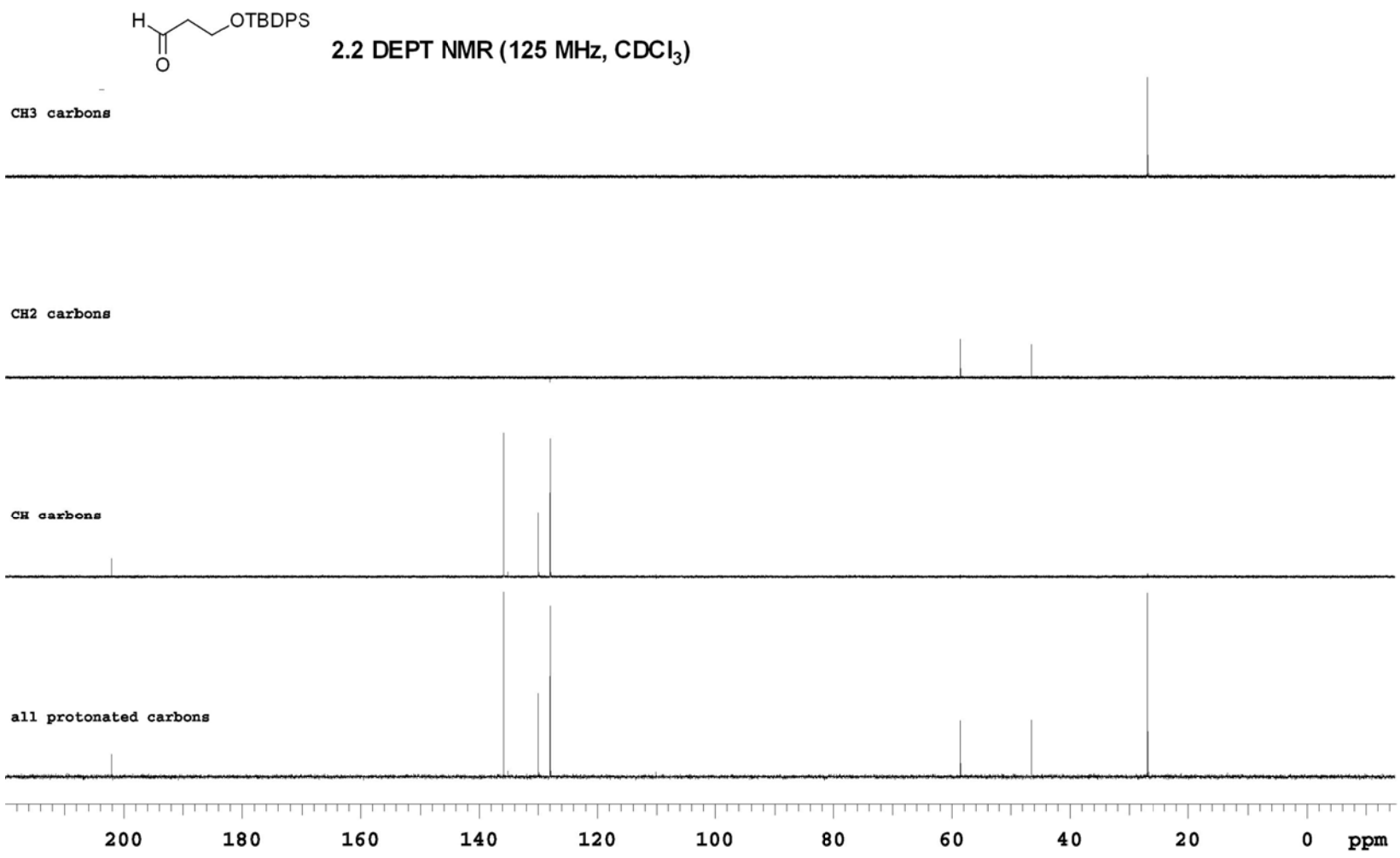
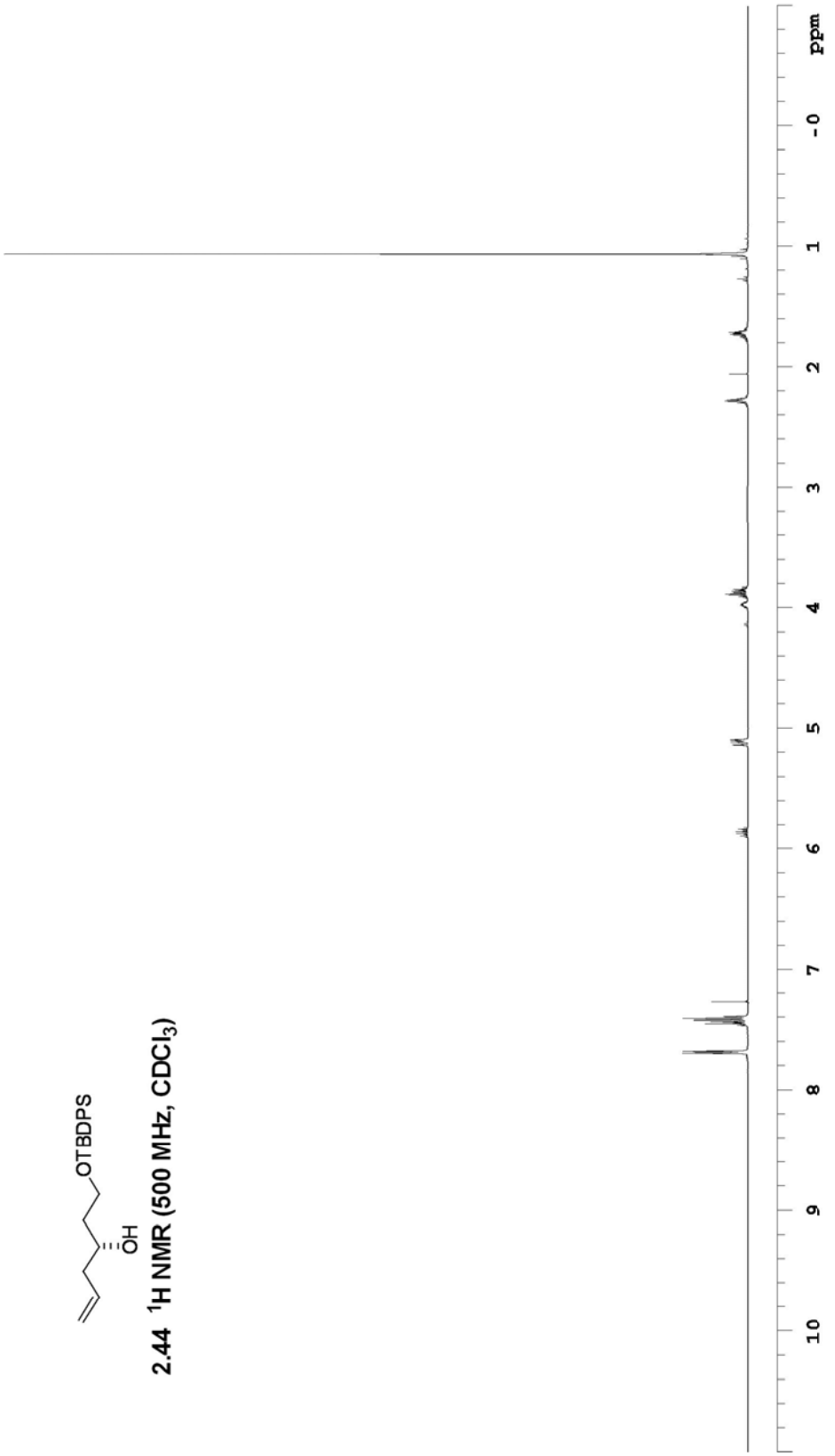

H
O
OTBDPS
2.2 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm



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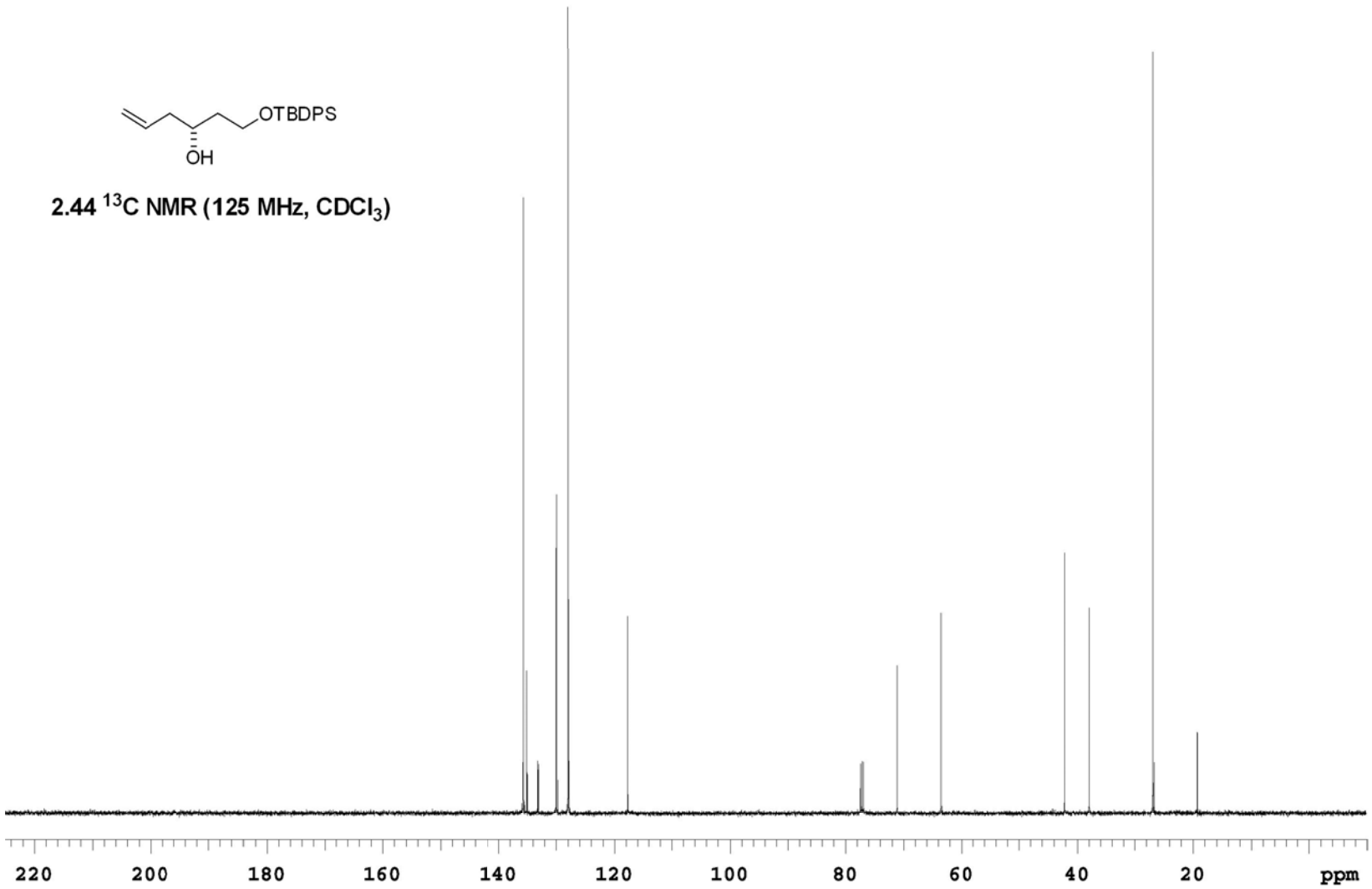
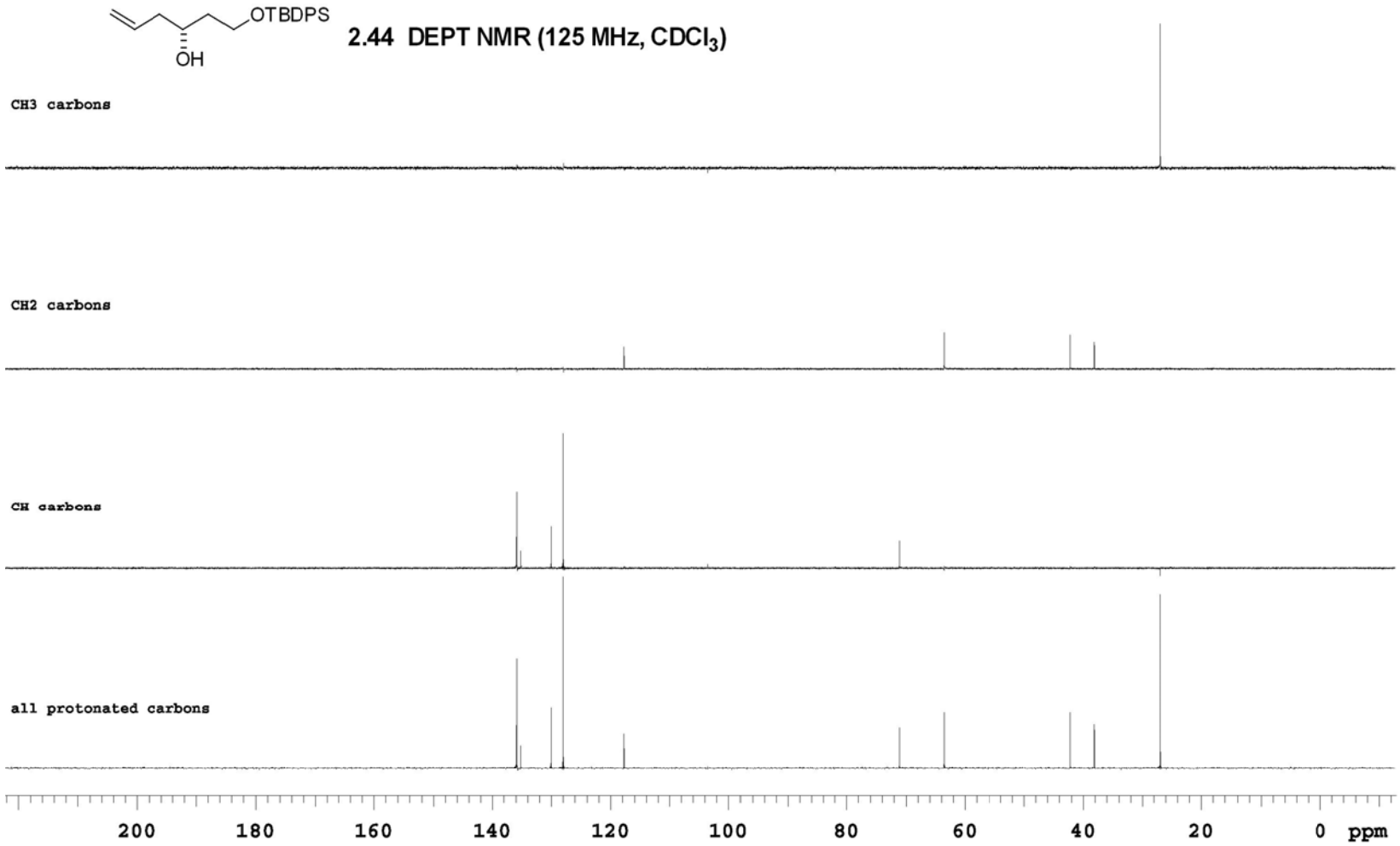
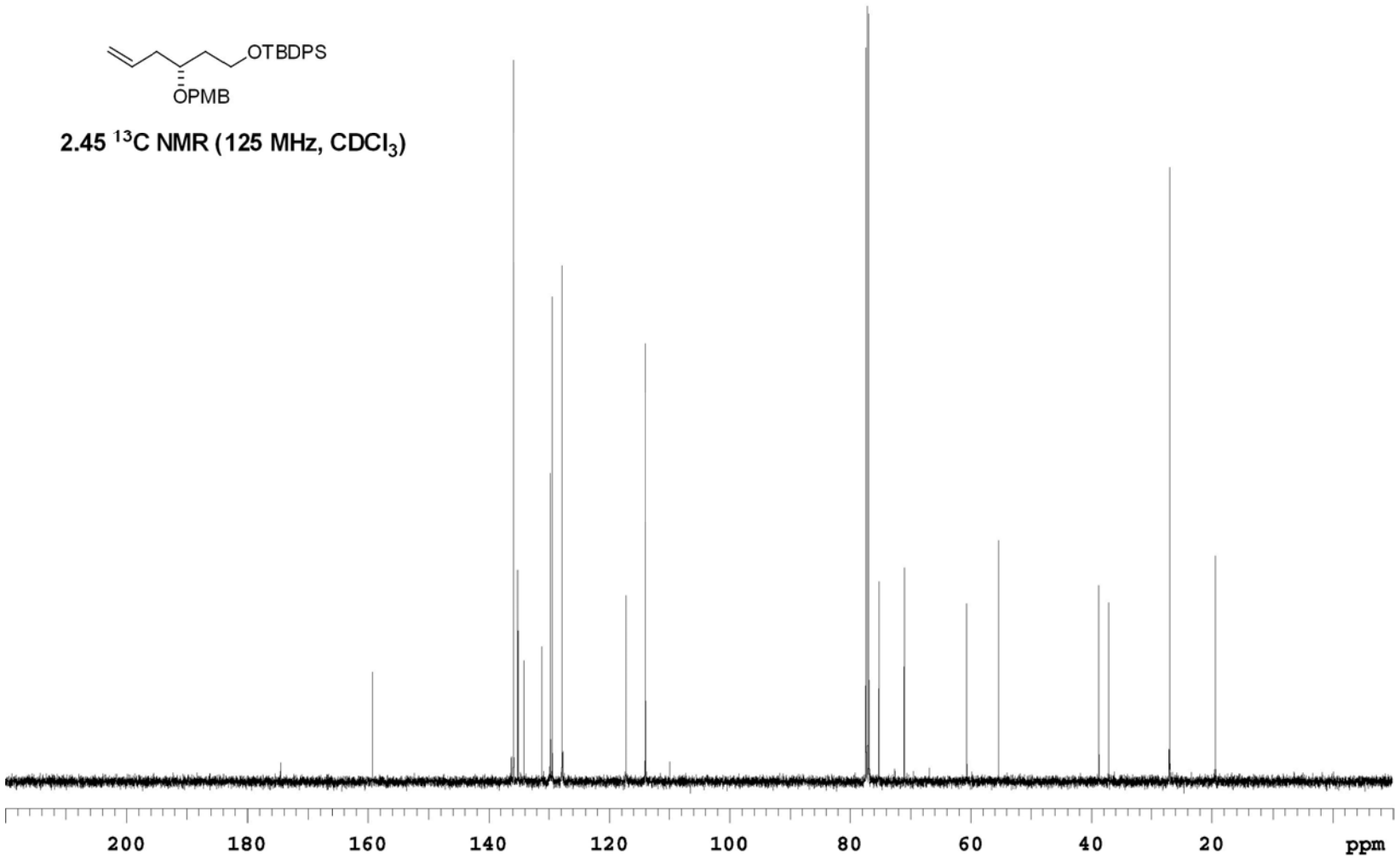


2.44 ^{13}C NMR (125 MHz, $CDCl_3$)


OTBDPS
OH
2.44 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

2.45 ^{1}H NMR (500 MHz, $CDCl_3$)


OTBDPS
OPMB
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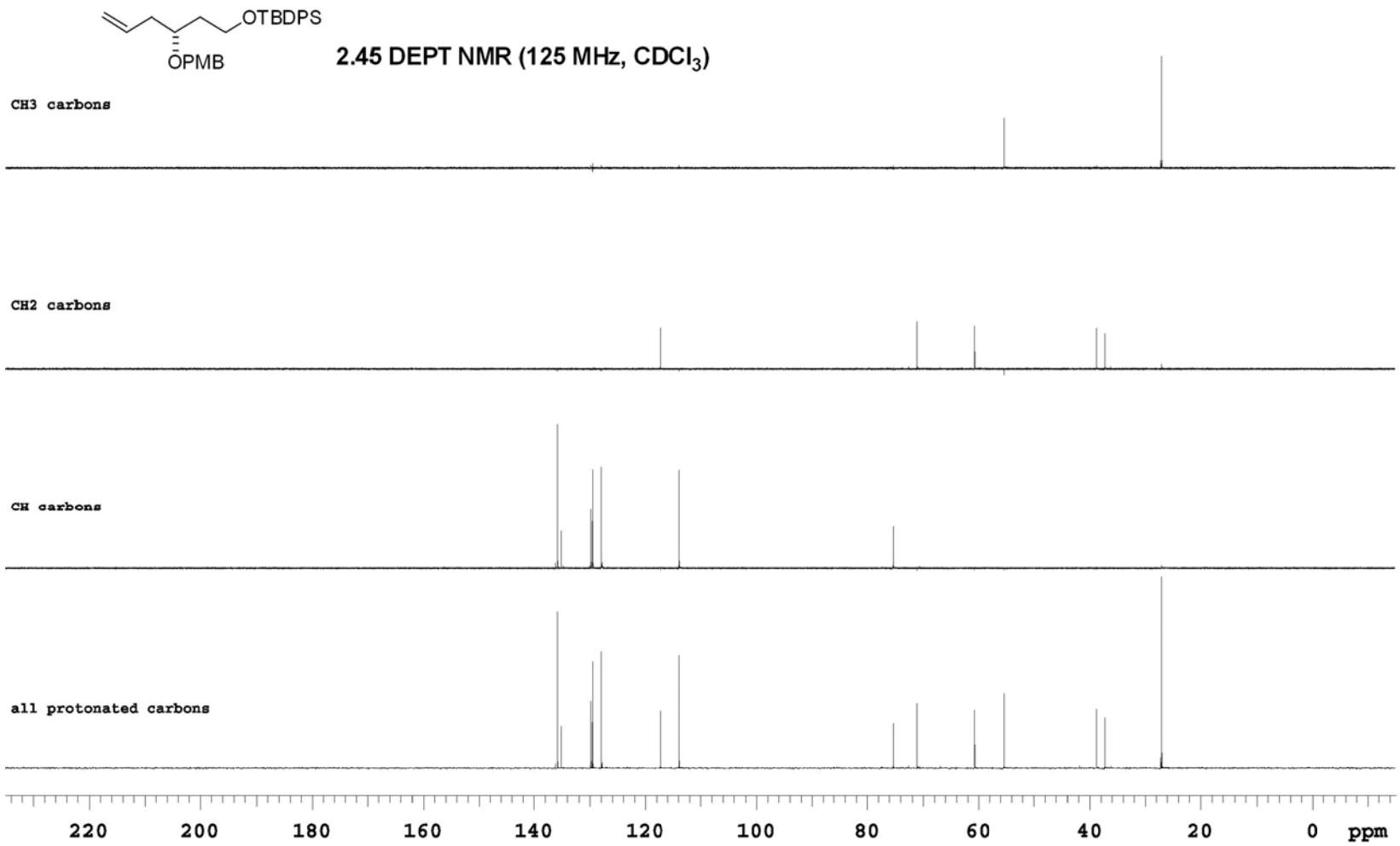
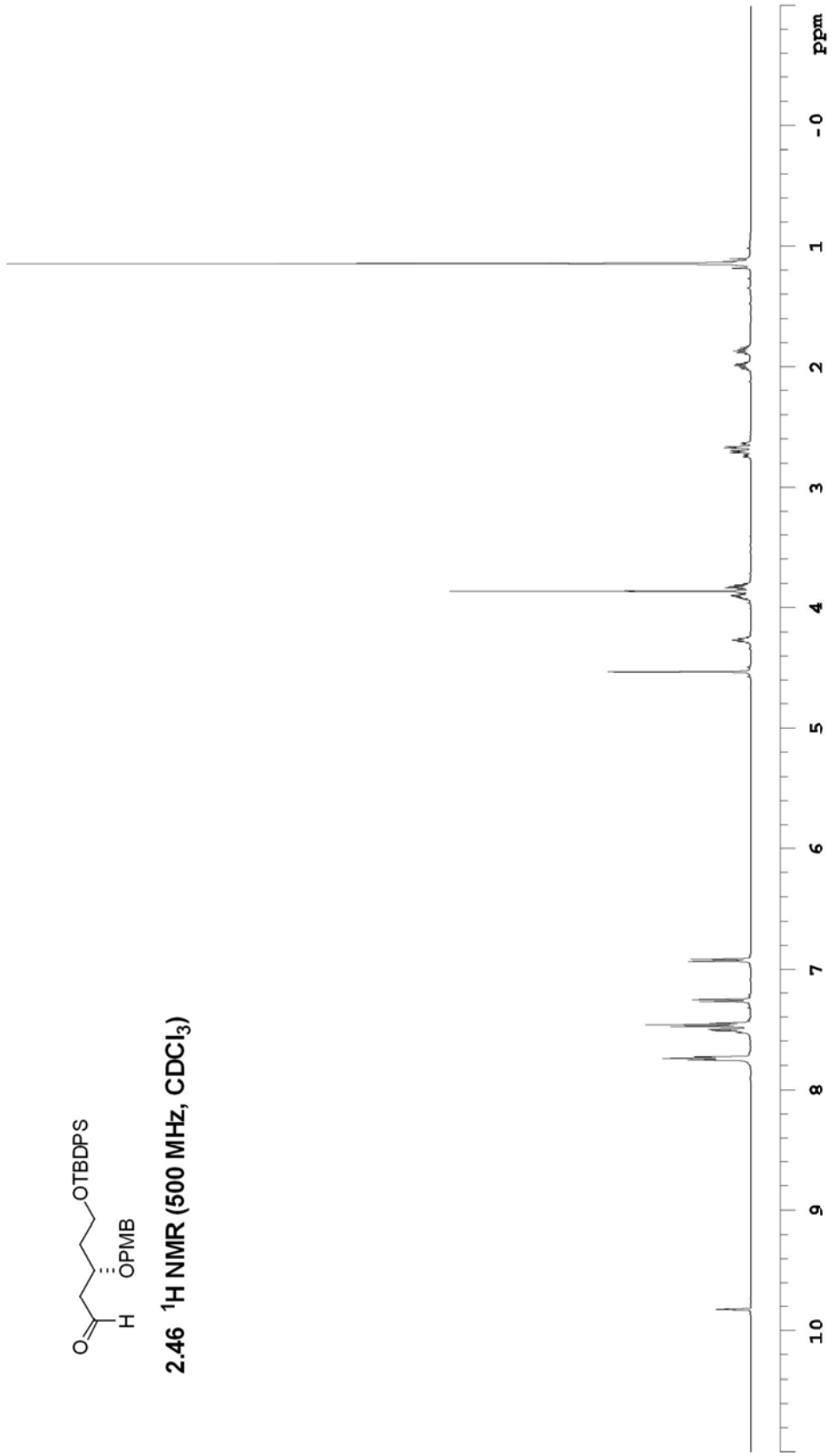
200
180
160
140
120
100
80
60
40
20
ppm


OTBDPS
OPMB
2.45 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
ppm



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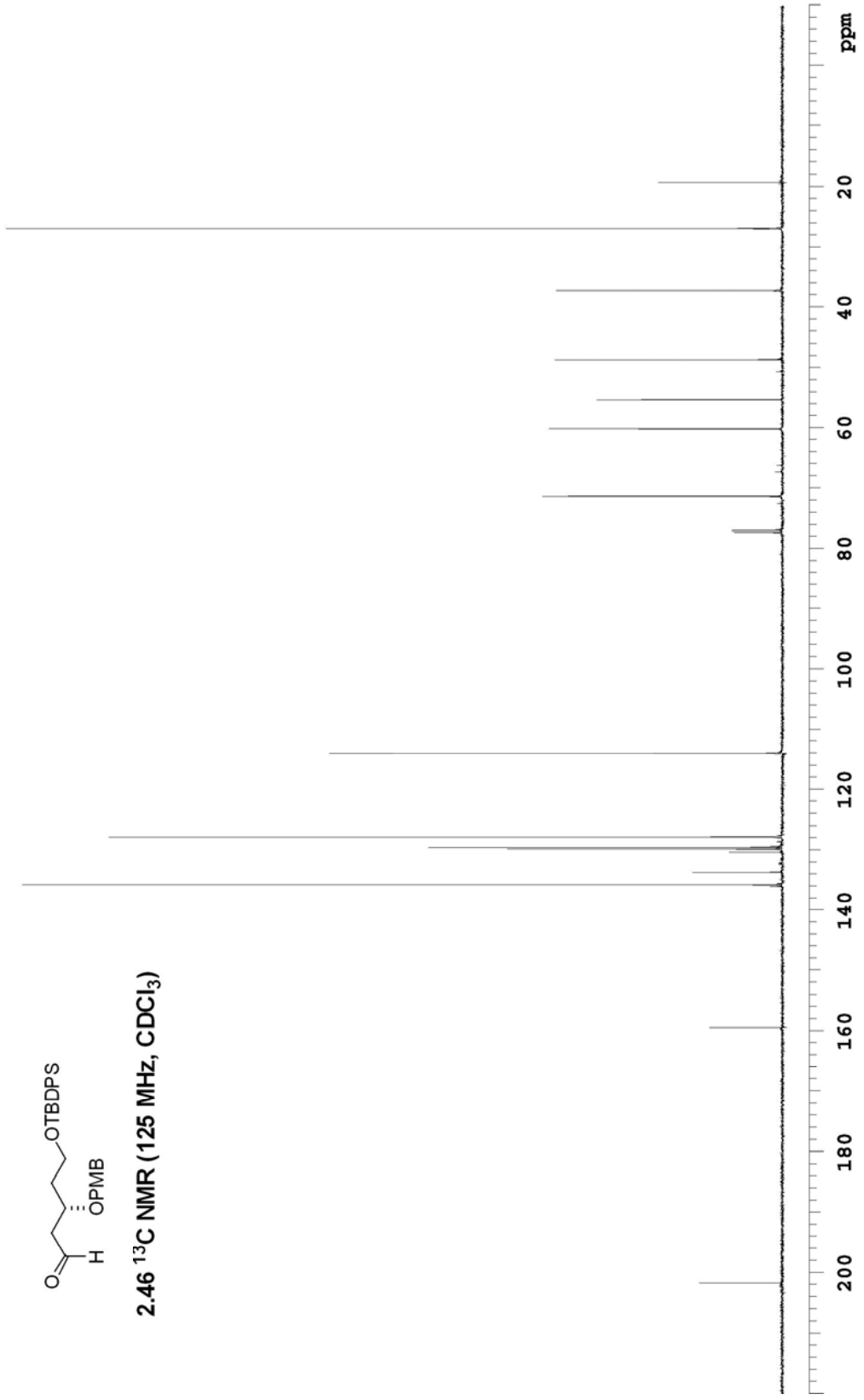
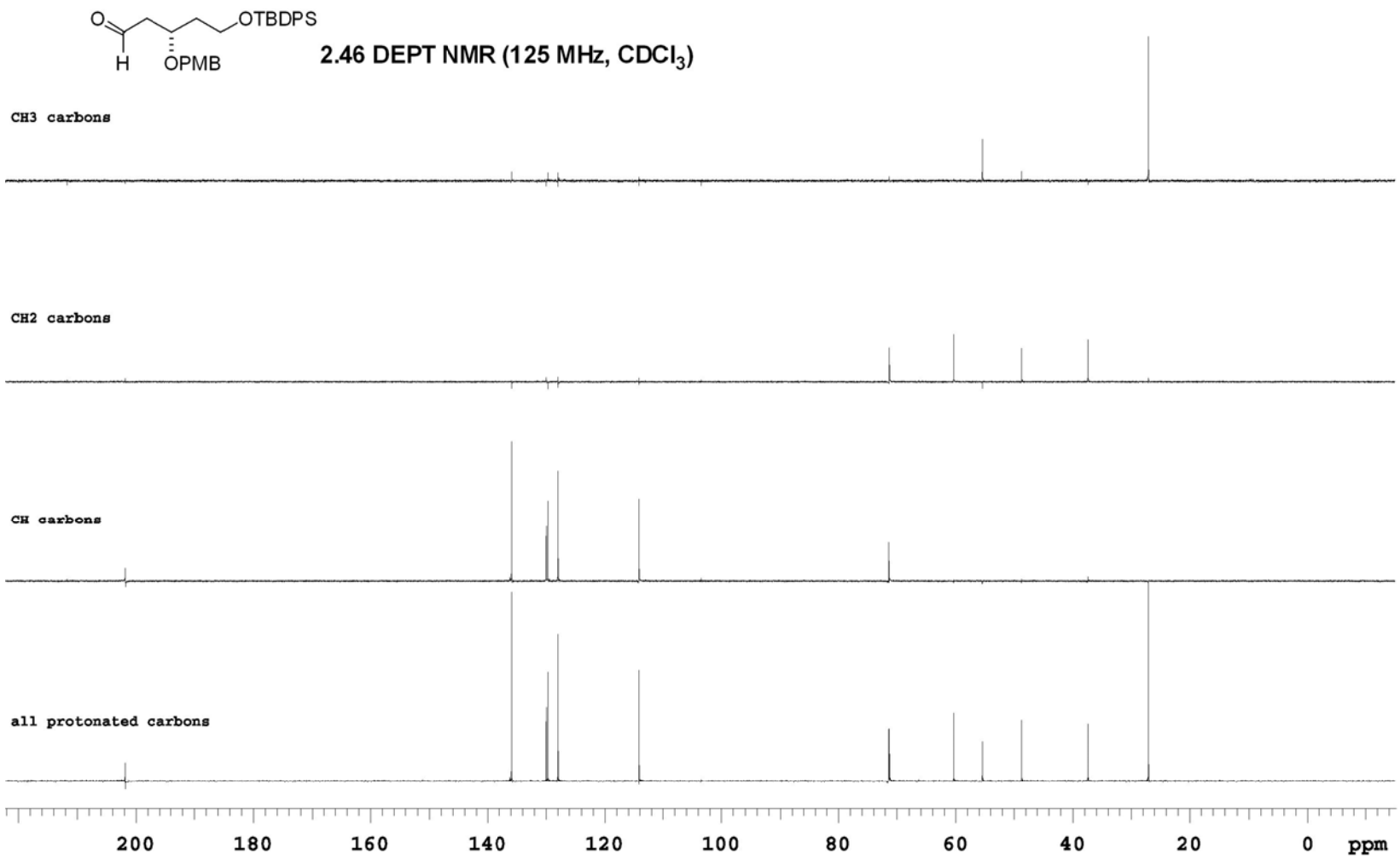
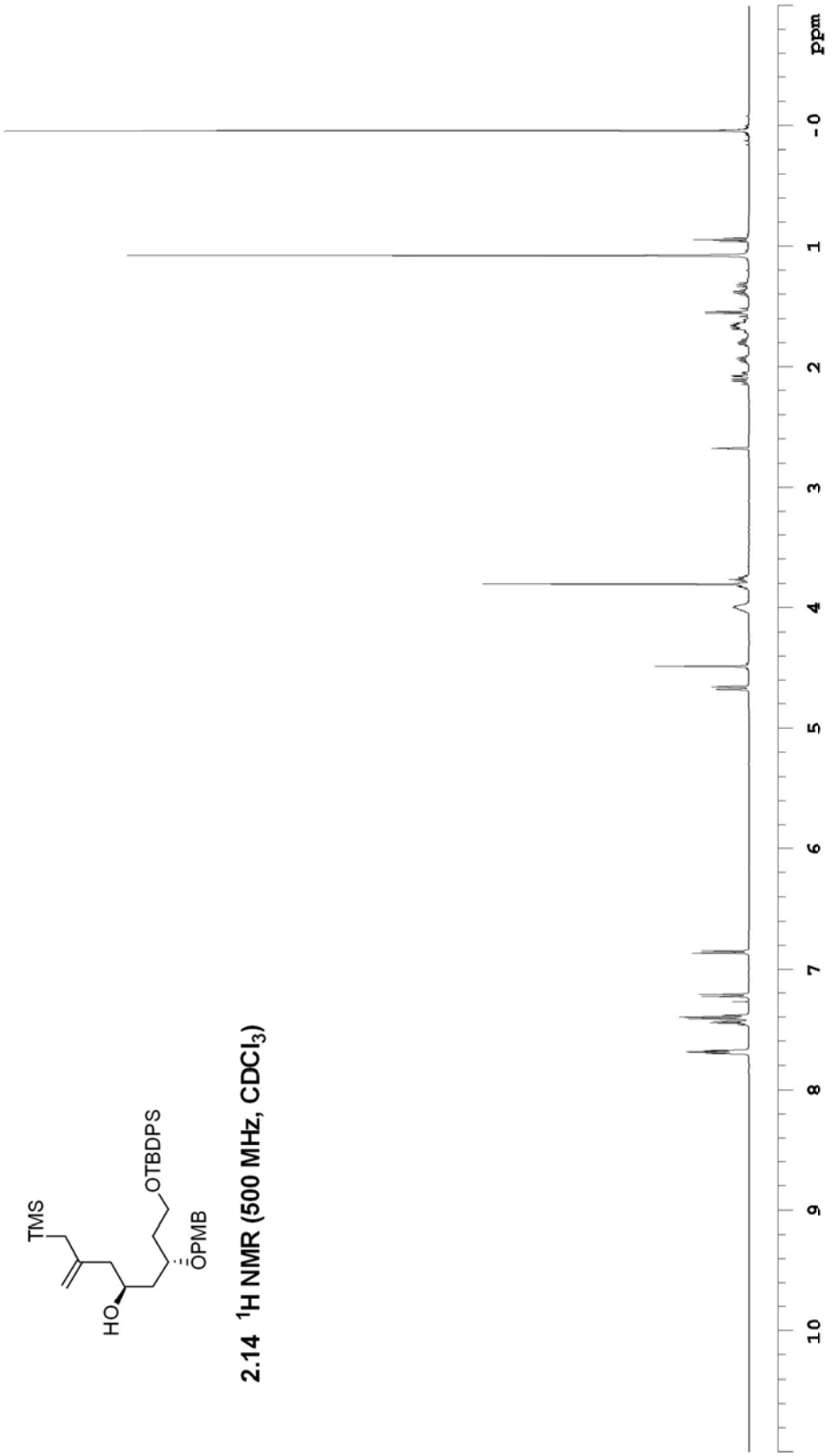


2.46 ^{13}C NMR (125 MHz, $CDCl_3$)


O
H
OPMB
OTBDPS
2.46 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm



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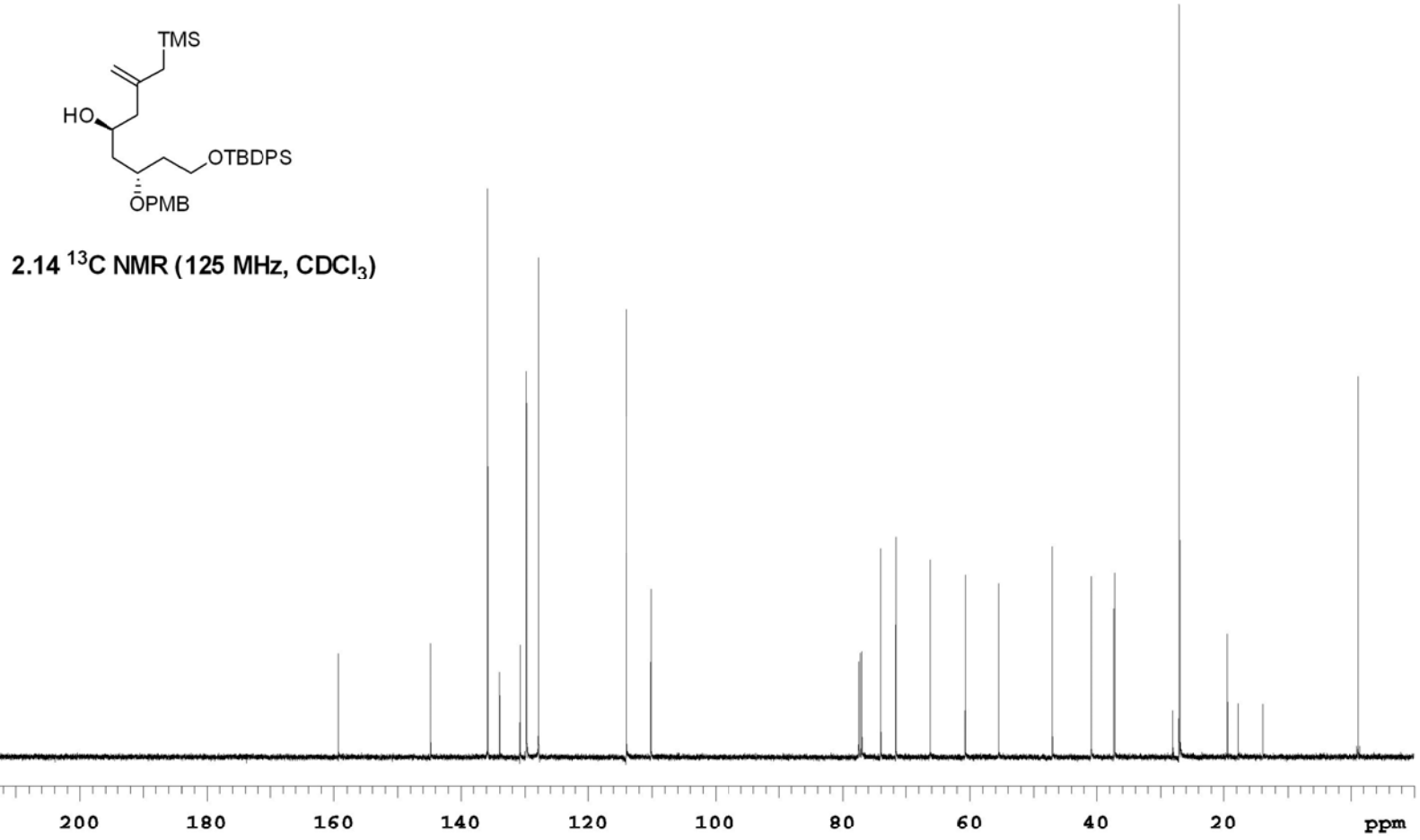
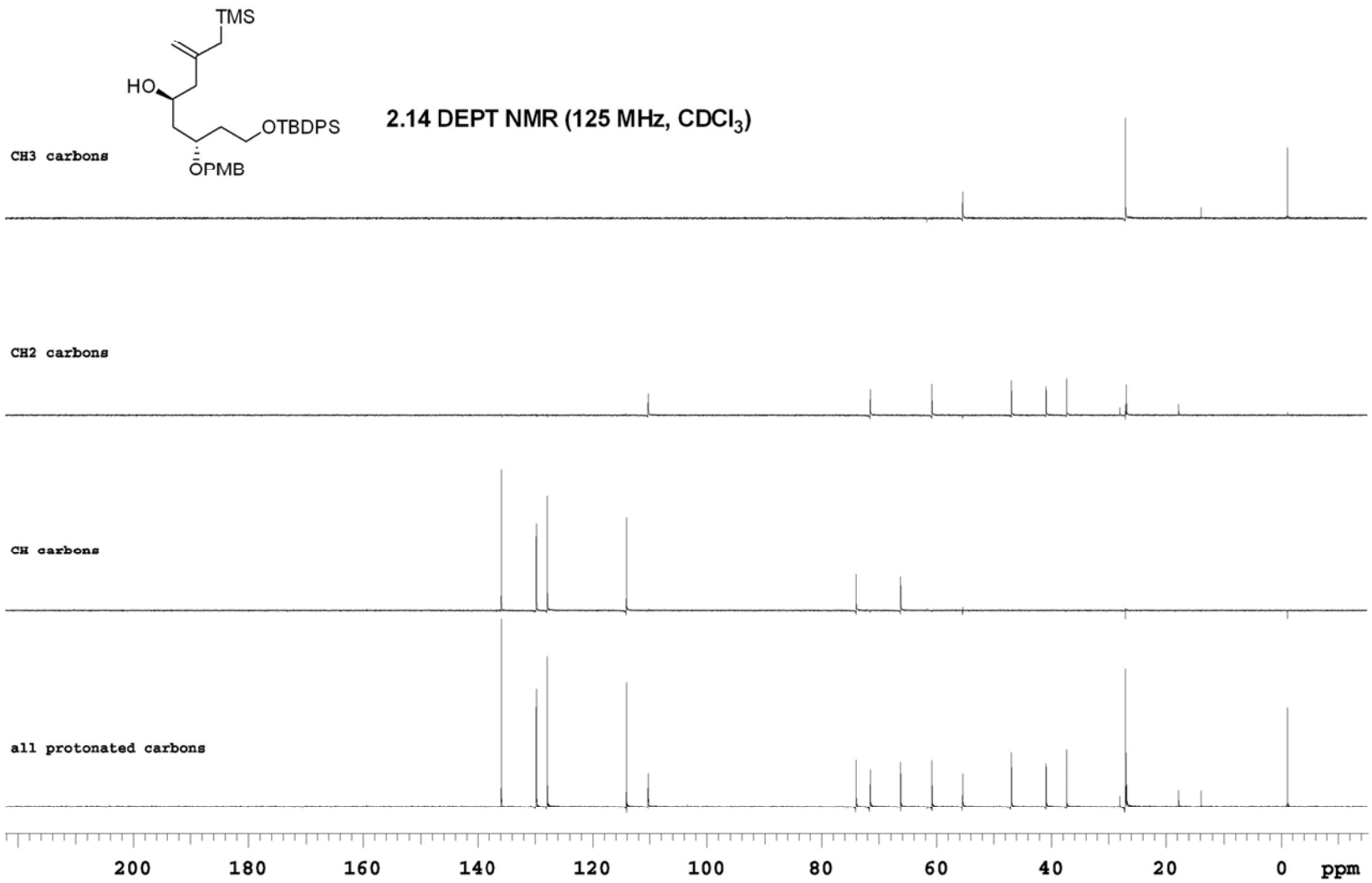


2.14 ^{13}C NMR (125 MHz, $CDCl_3$)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HO
OTBDPS
OPMB
2.14 DEPT NMR (125 MHz, CDCl3)
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CH2 carbons
CH carbons
all protonated carbons
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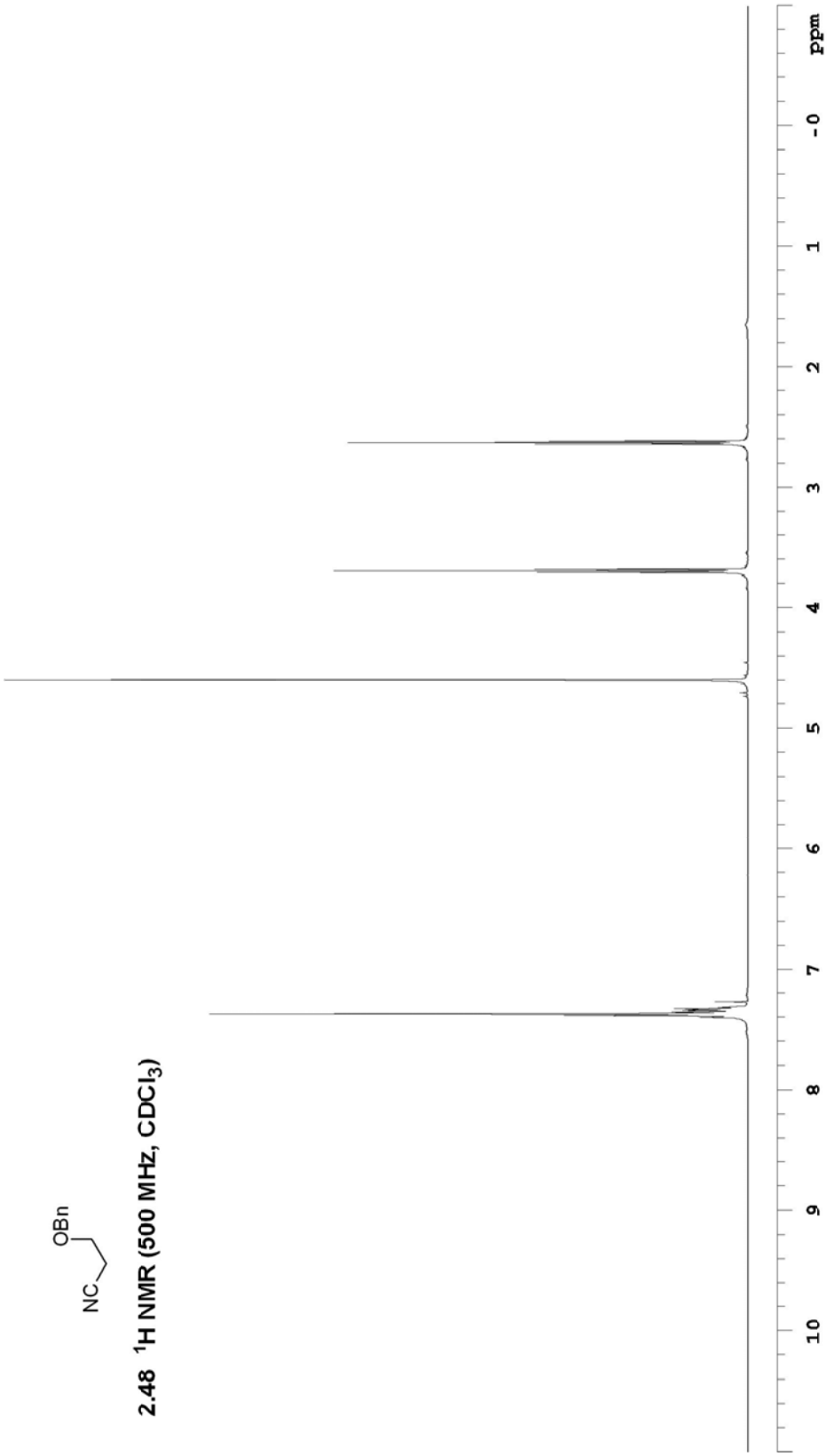
180
160
140
120
100
80
60
40
20
0
ppm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NC
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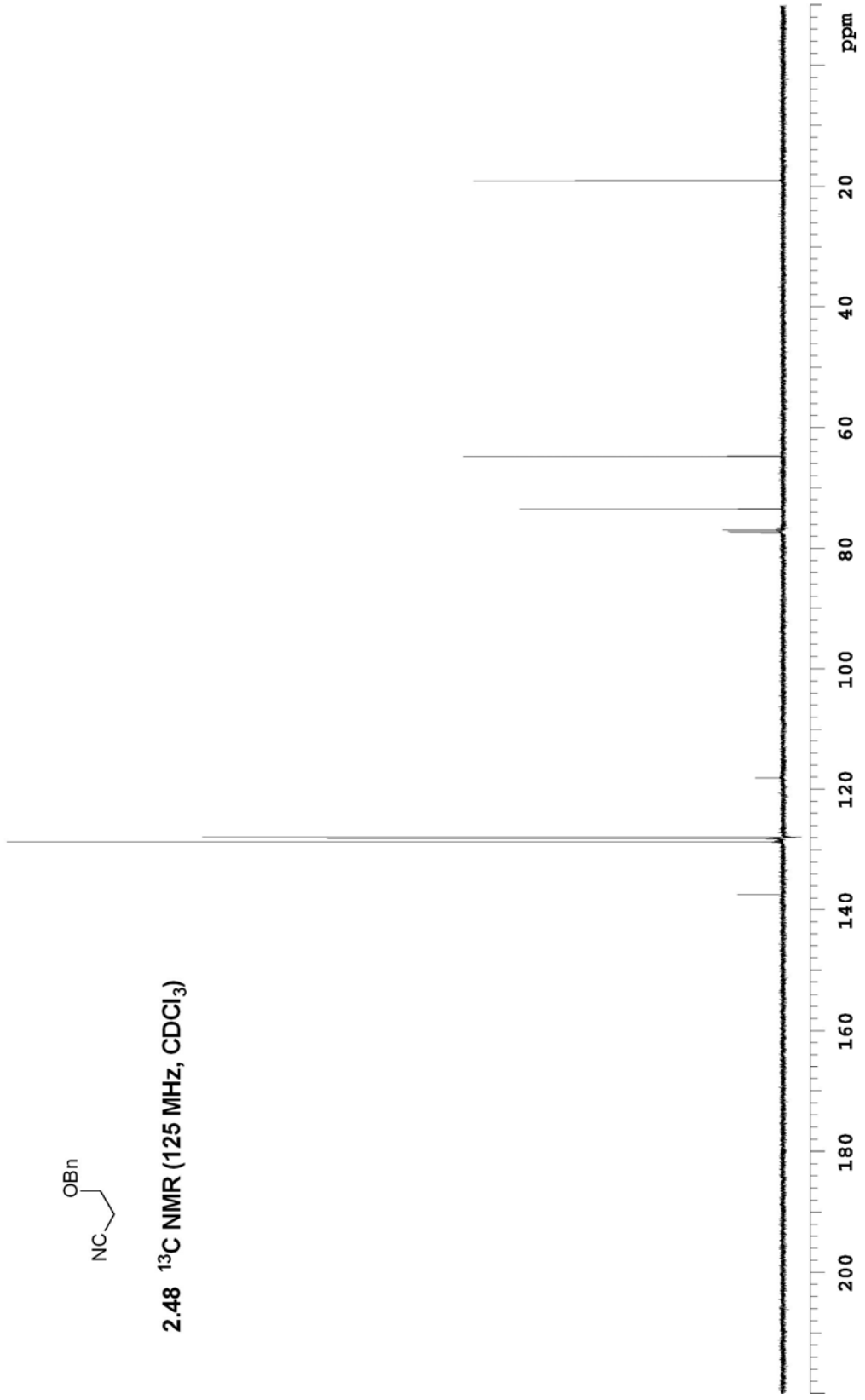
10
9
8
7
6
5
4
3
2
1
-0
ppm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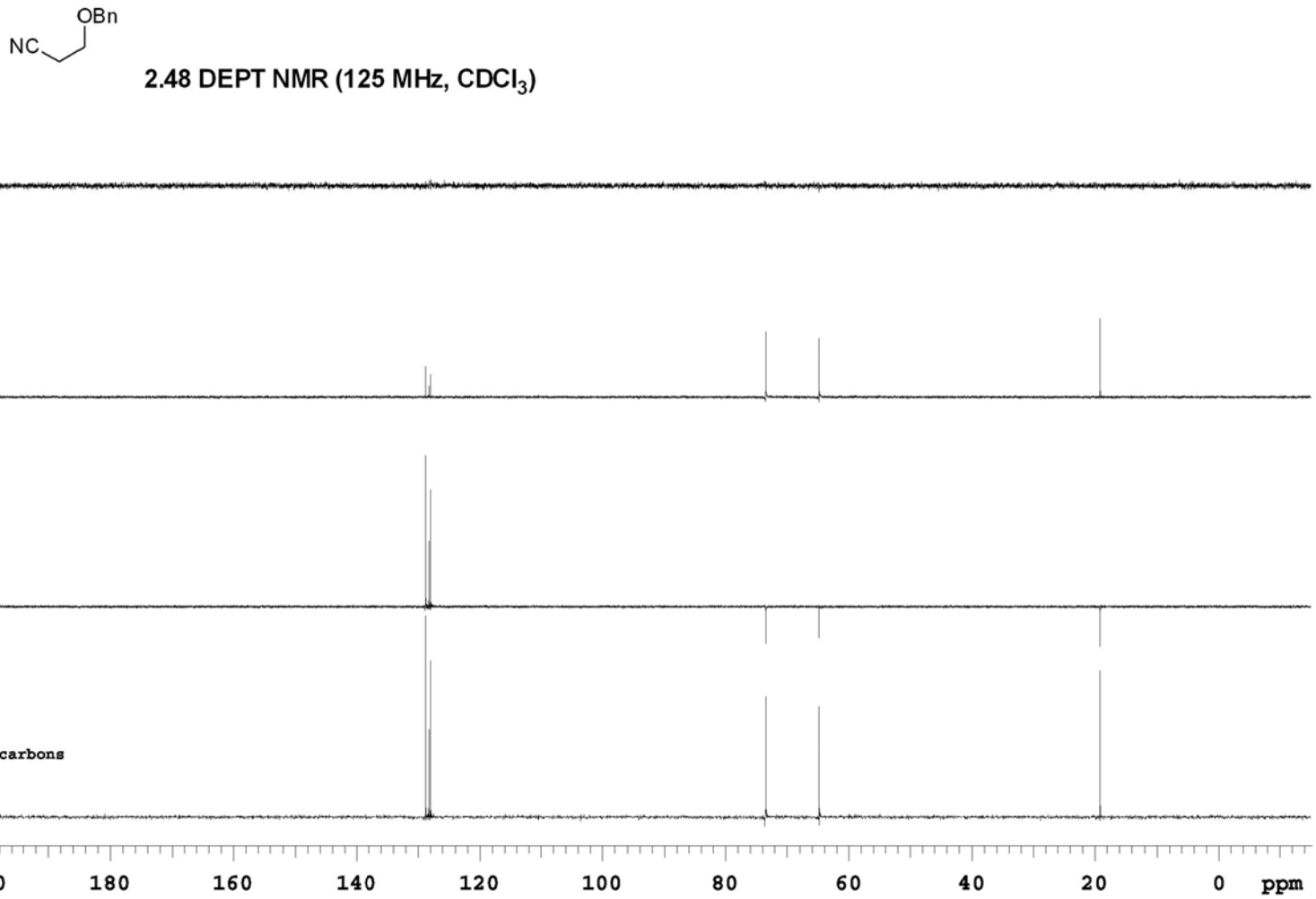
NC
2.48 ^{13}C NMR (125 MHz, $CDCl_3$)
200
180
160
140
120
100
80
60
40
20
ppm


OBn
NC
2.48 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
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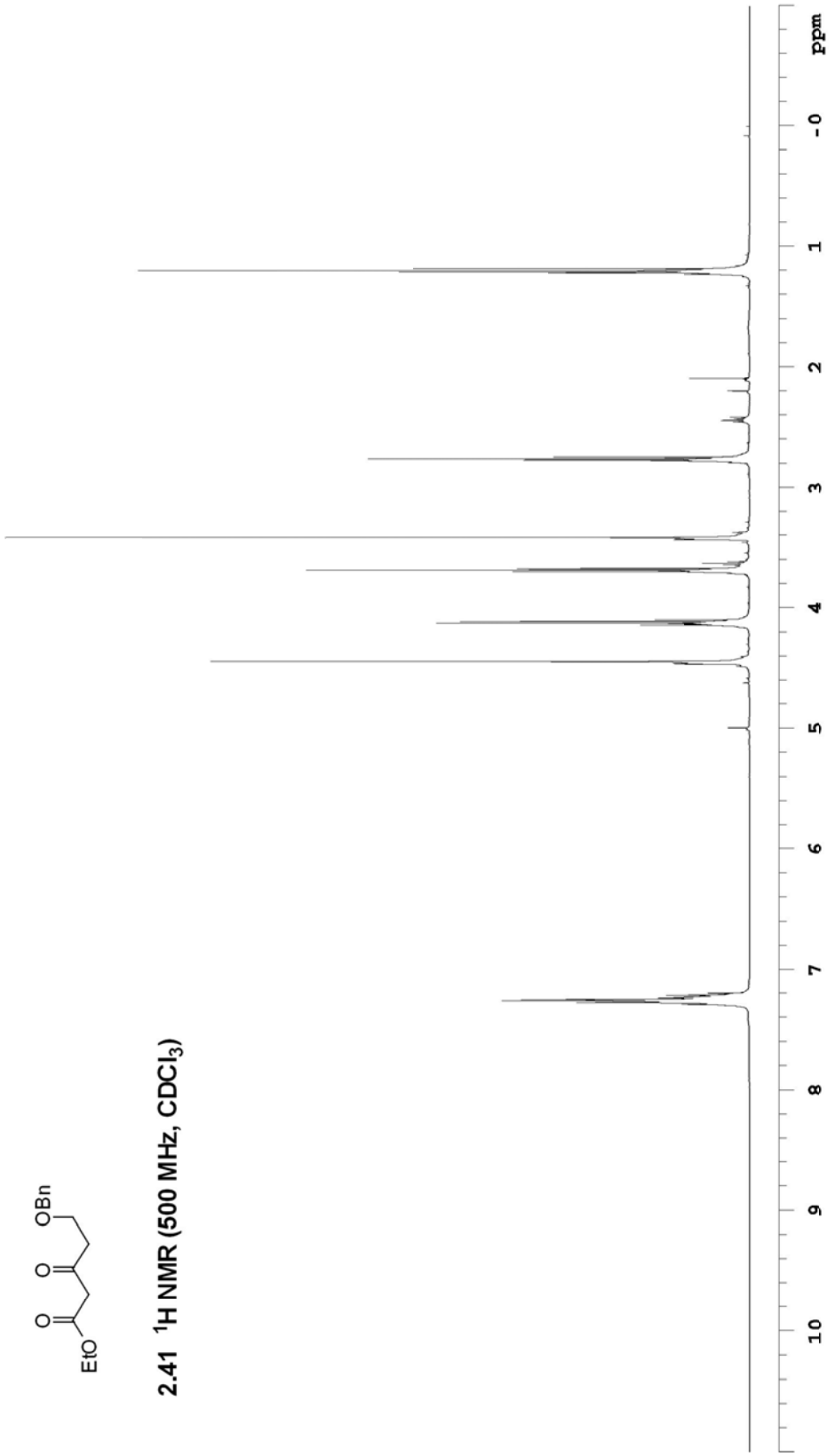
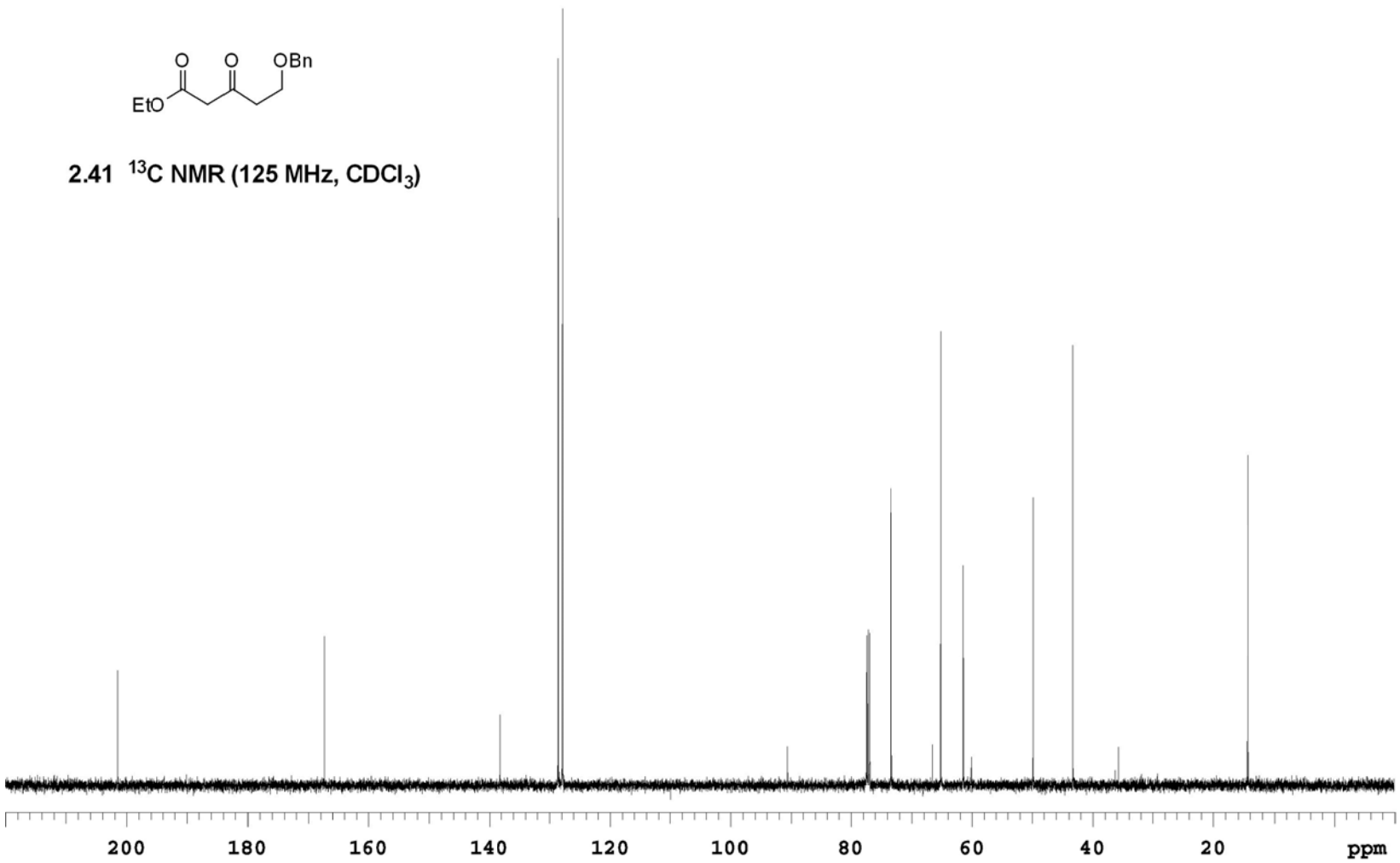
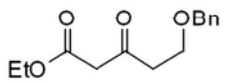
180
160
140
120
100
80
60
40
20
0
ppm

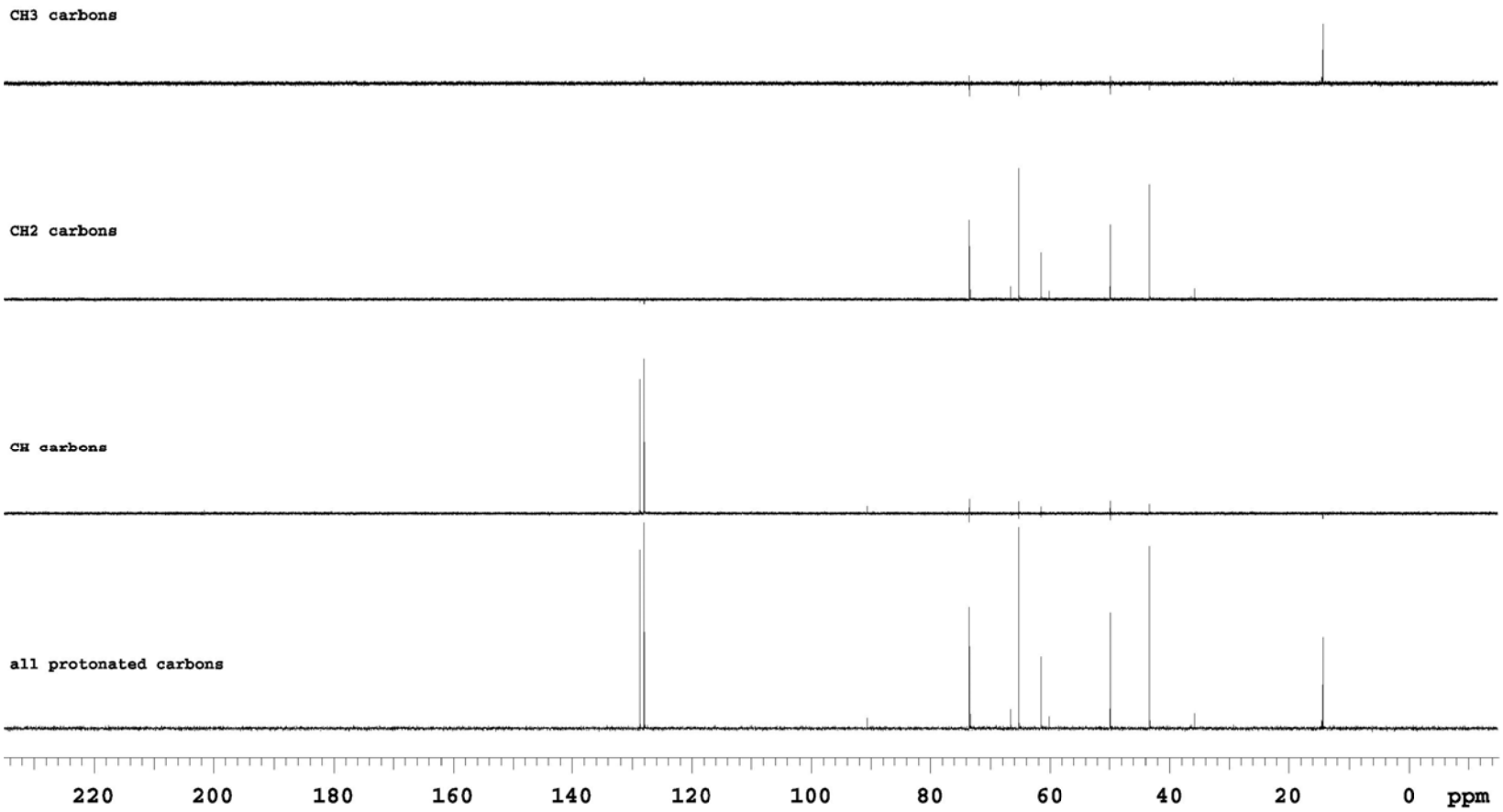


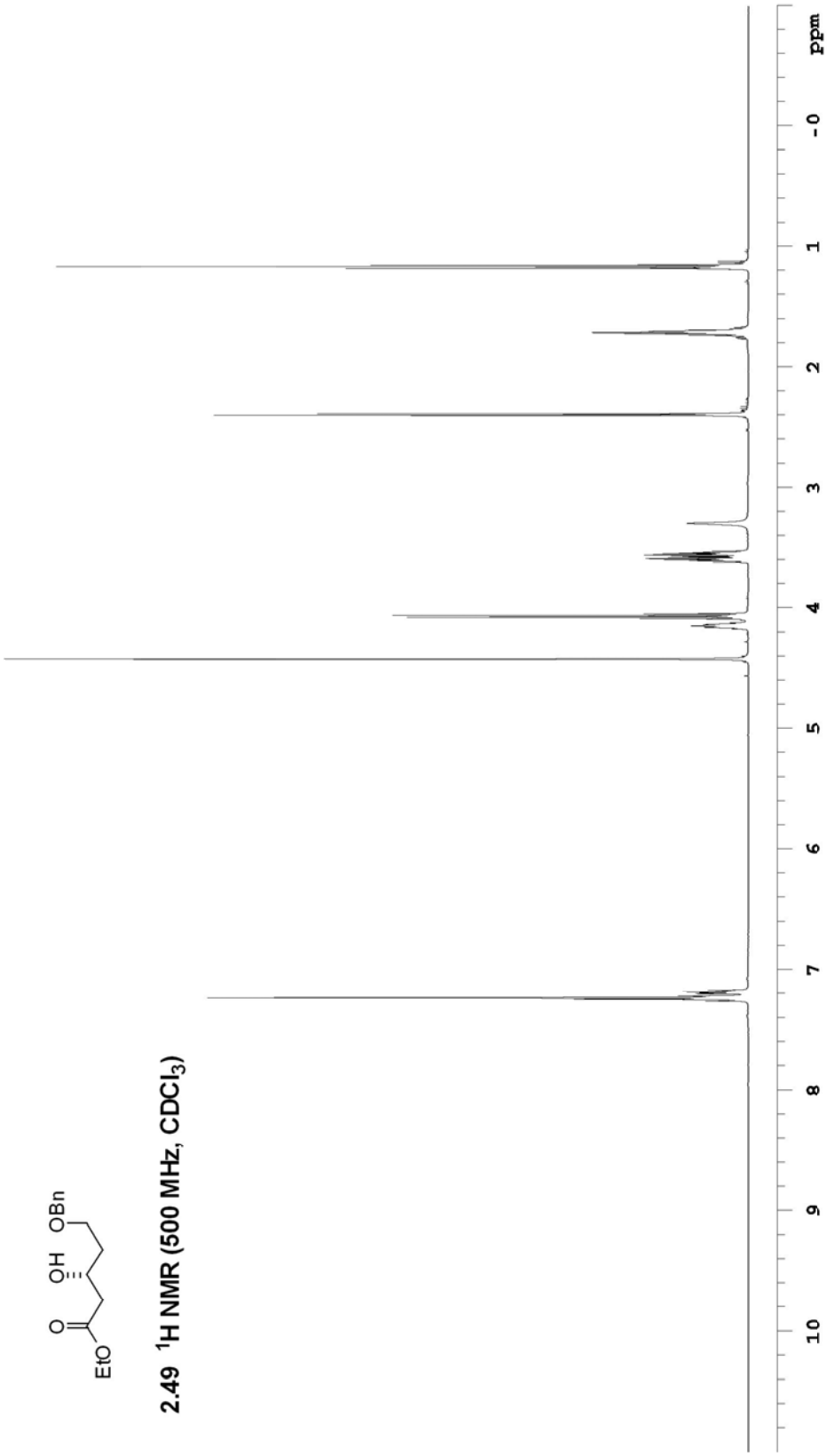
2.41 ^{1}H NMR (500 MHz, $CDCl_3$)


O
O
OBn
EtO
2.41 ^{13}C NMR (125 MHz, $CDCl_3$)
200
180
160
140
120
100
80
60
40
20
ppm



2.41 DEPT NMR (125 MHz, $CDCl_3$)





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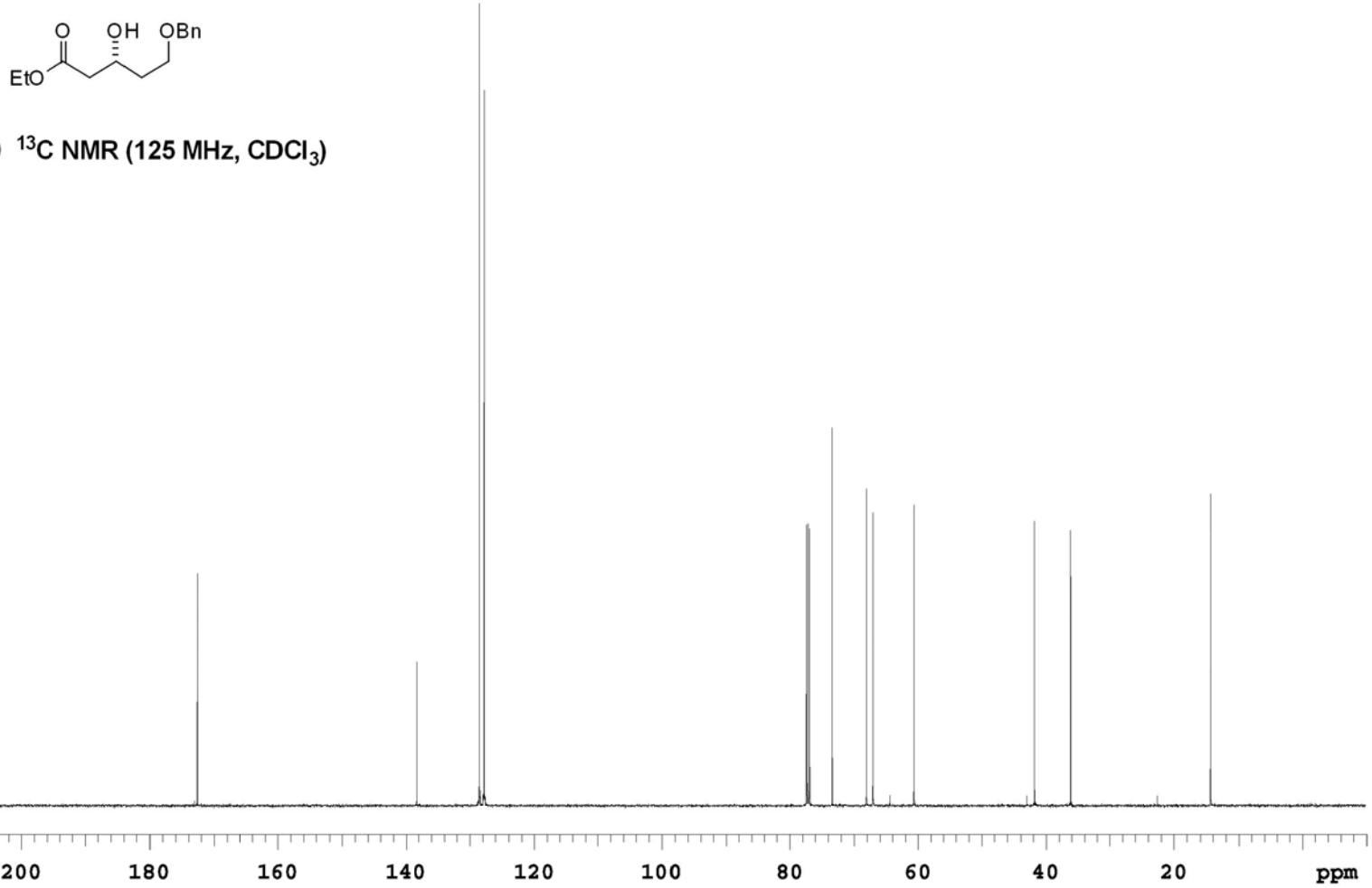
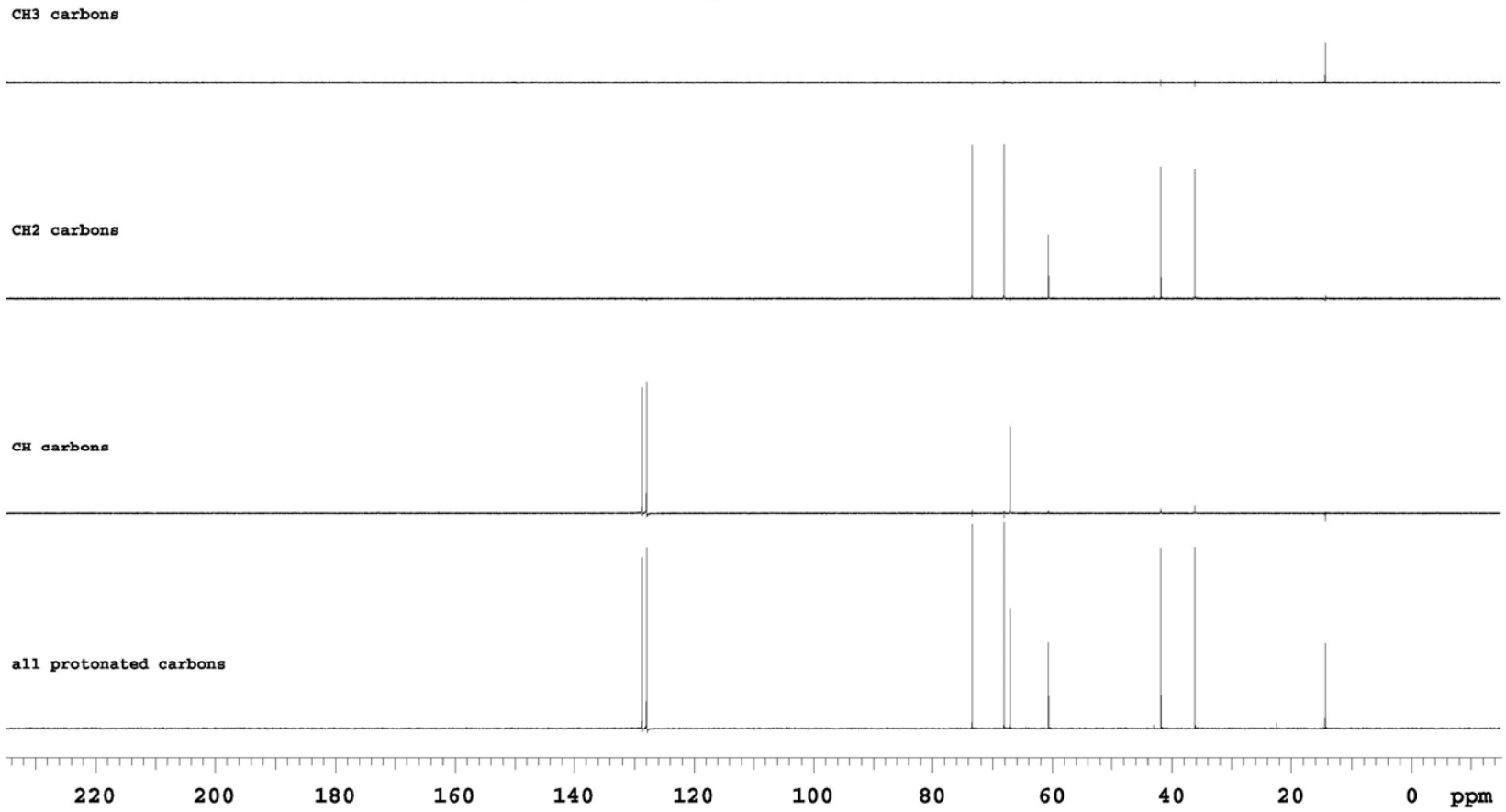
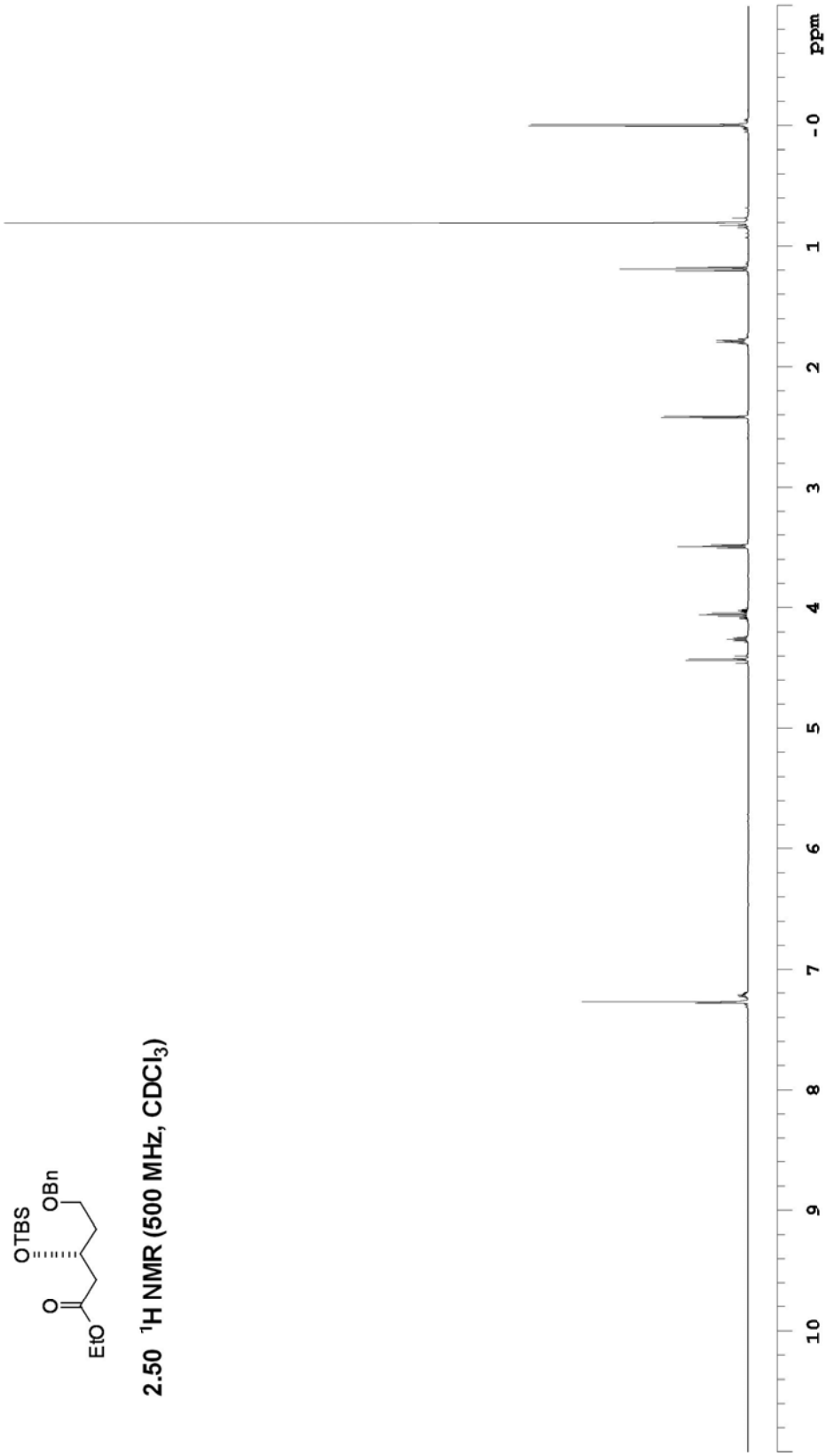


2.49 ^{13}C NMR (125 MHz, $CDCl_3$)

2.49 DEPT NMR (125 MHz, $CDCl_3$)





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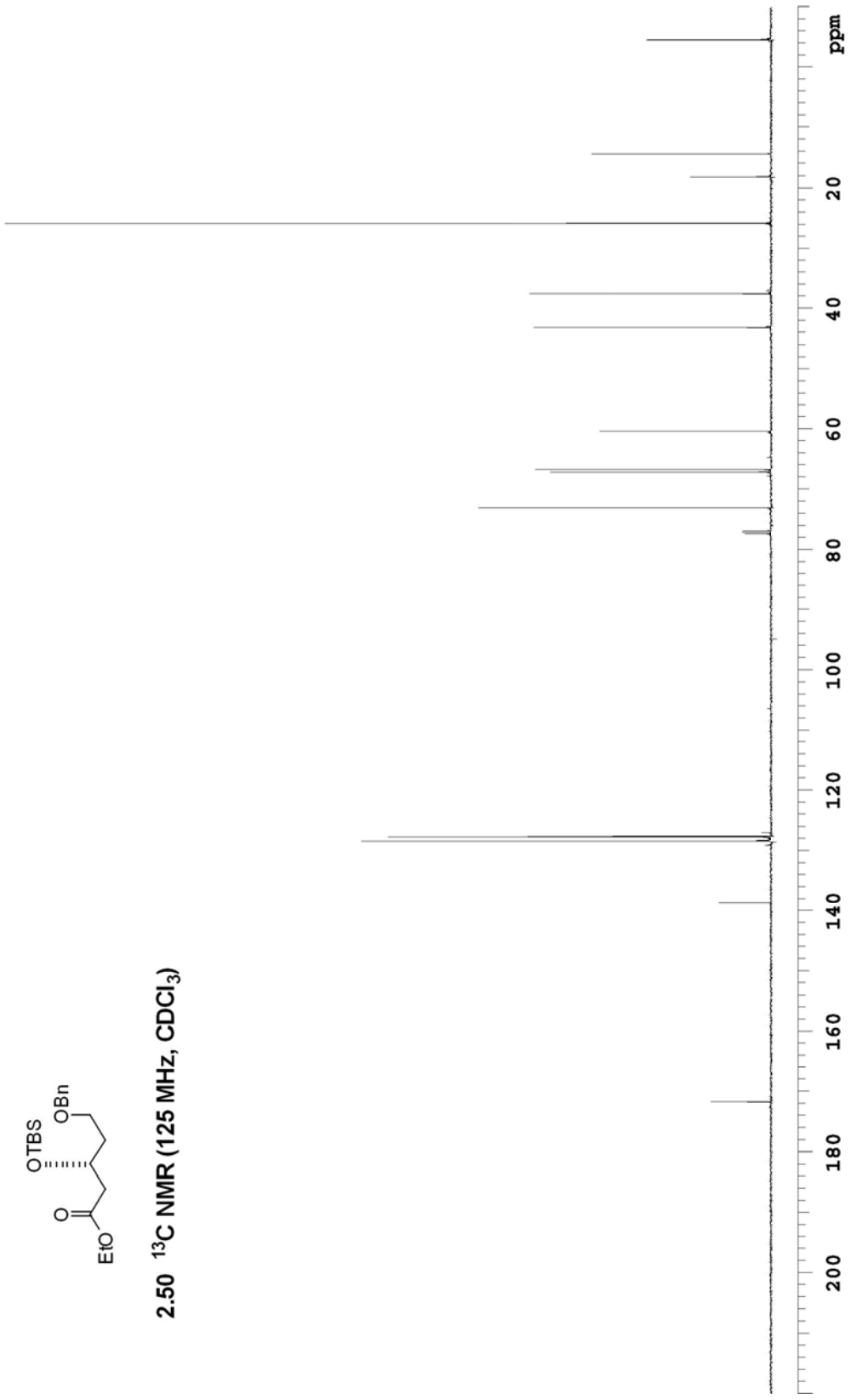

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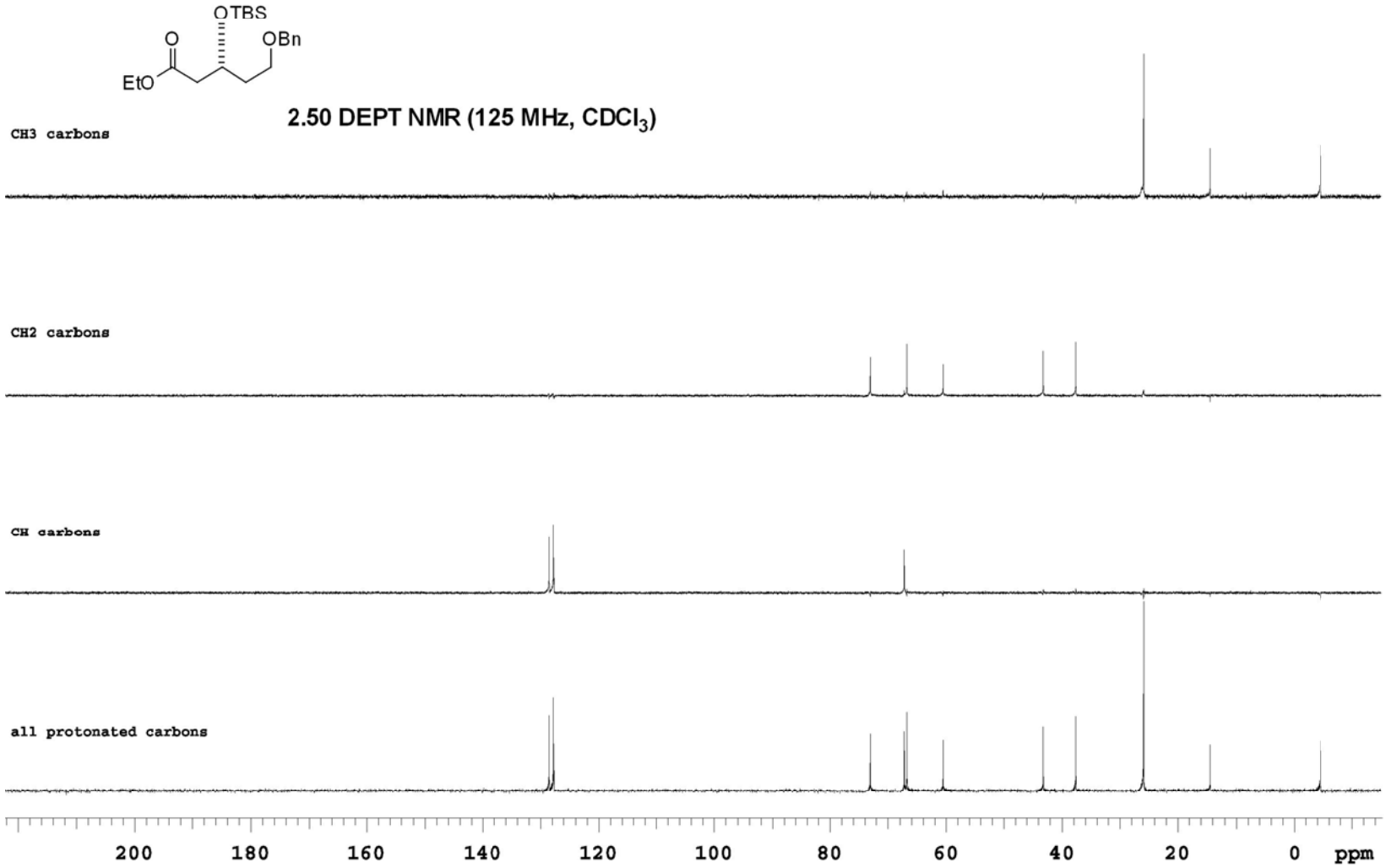
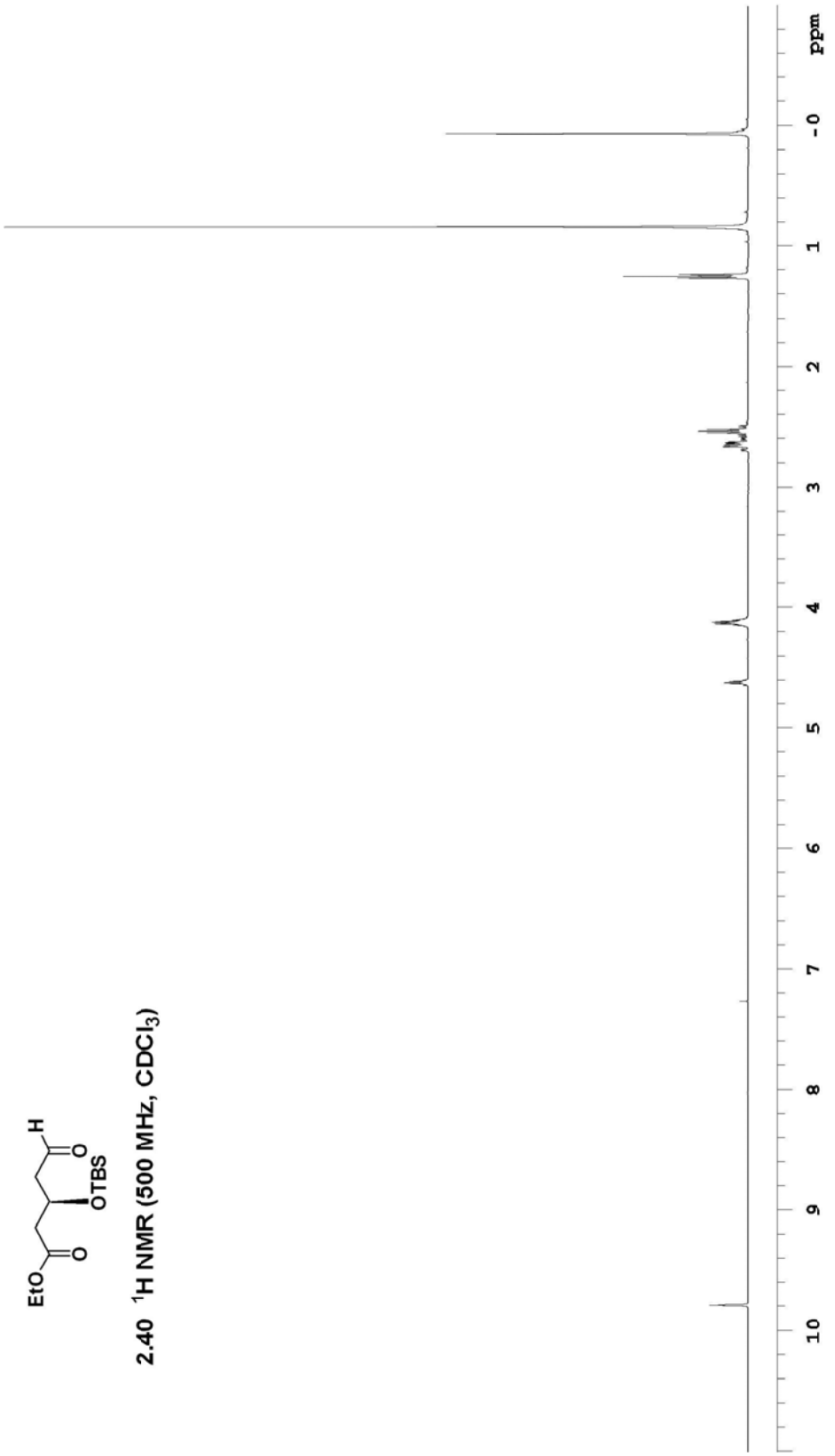
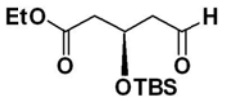
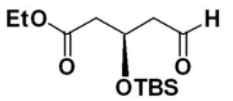

OTBS
O
OBn
EtO
2.50 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm



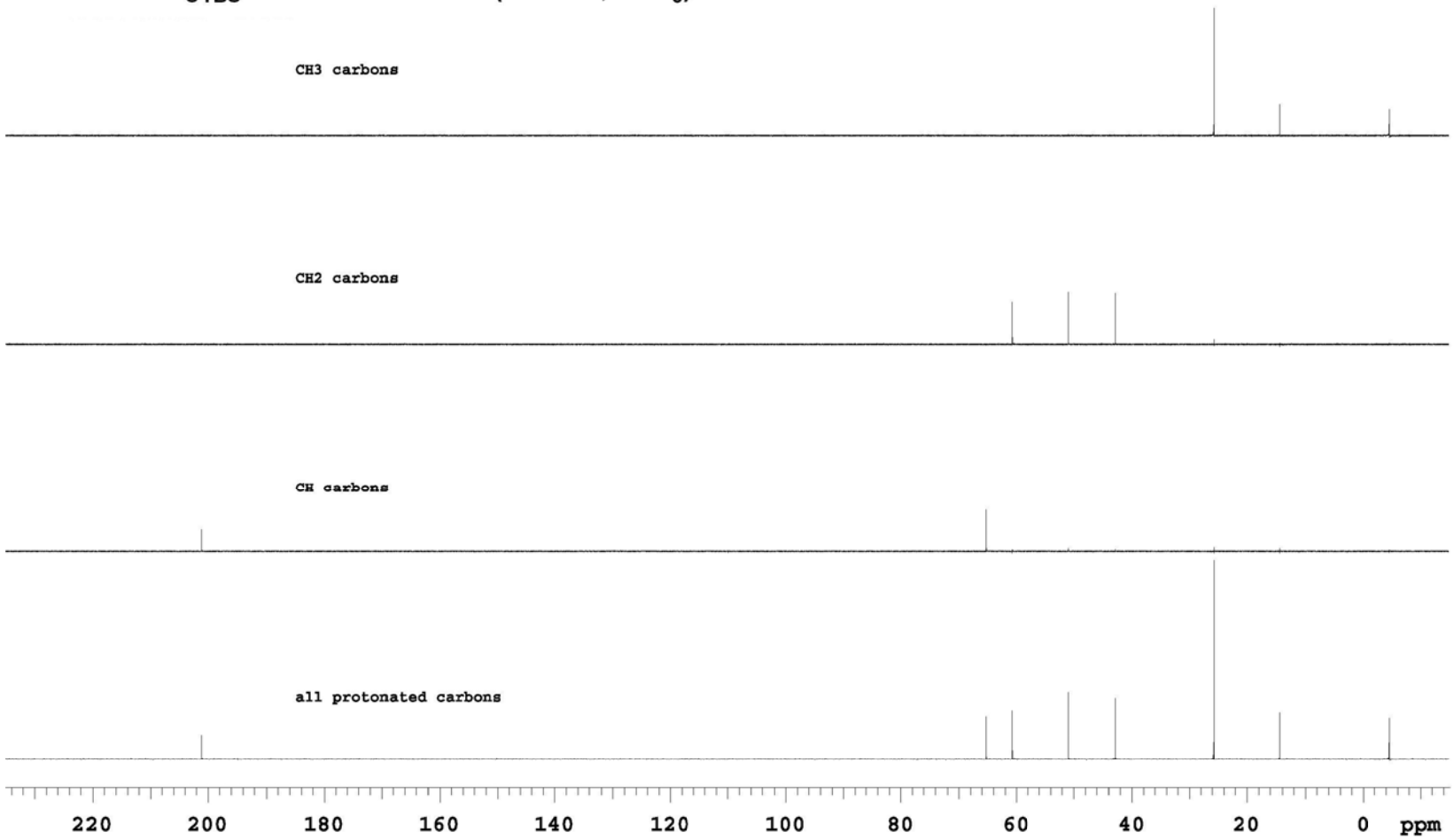
2.40 ^{1}H NMR (500 MHz, $CDCl_3$)

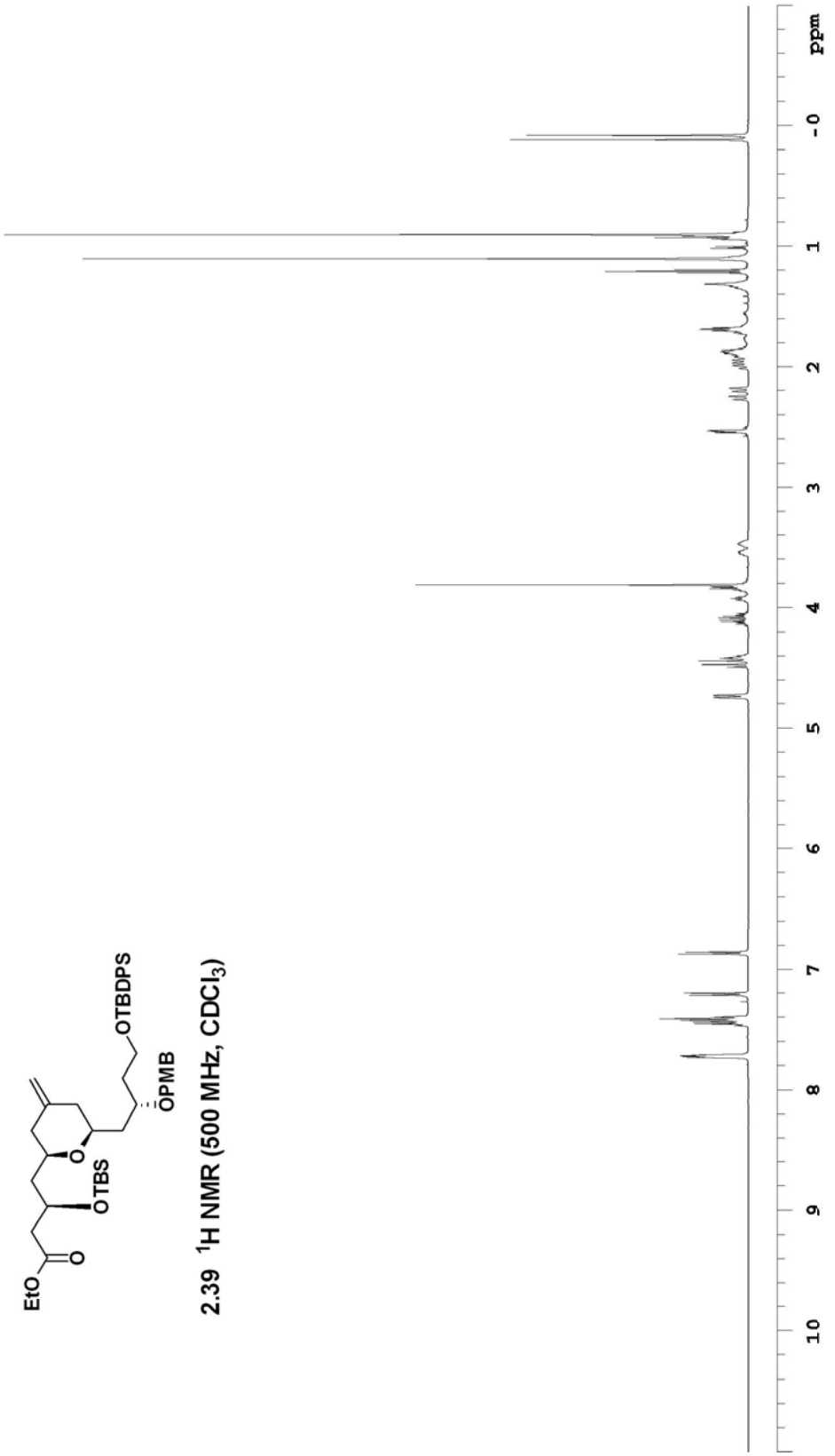


2.40 ^{13}C NMR (125 MHz, $CDCl_3$)

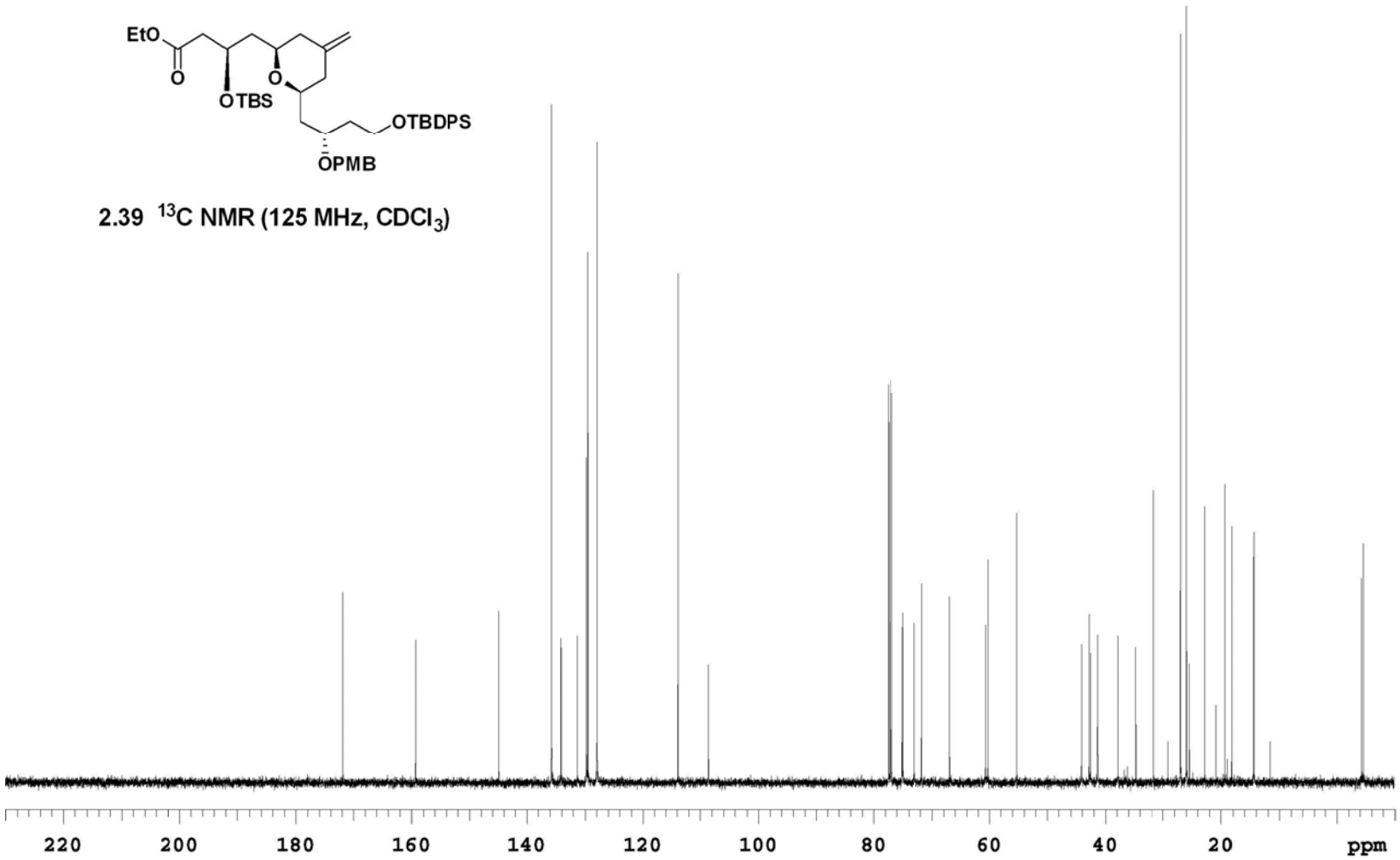


2.40 DEPT NMR (125 MHz, $CDCl_3$)

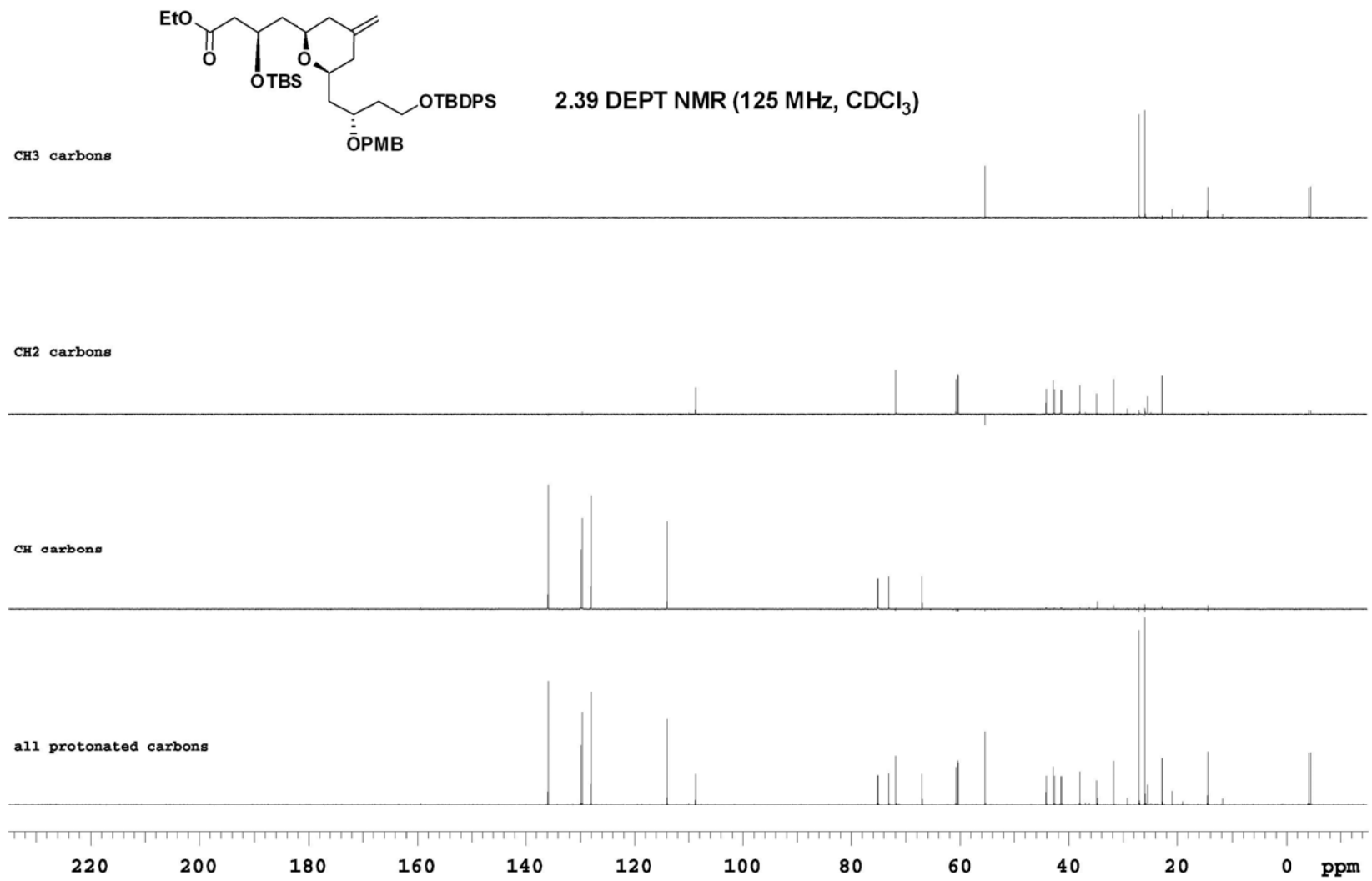


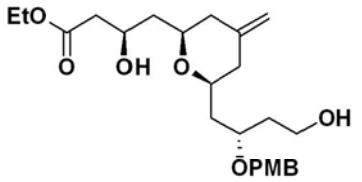


2.39 ^{1}H NMR (500 MHz, $CDCl_3$)

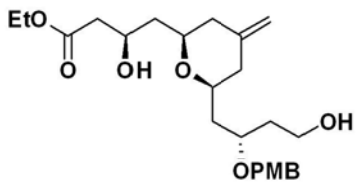


2.39 ^{13}C NMR (125 MHz, $CDCl_3$)

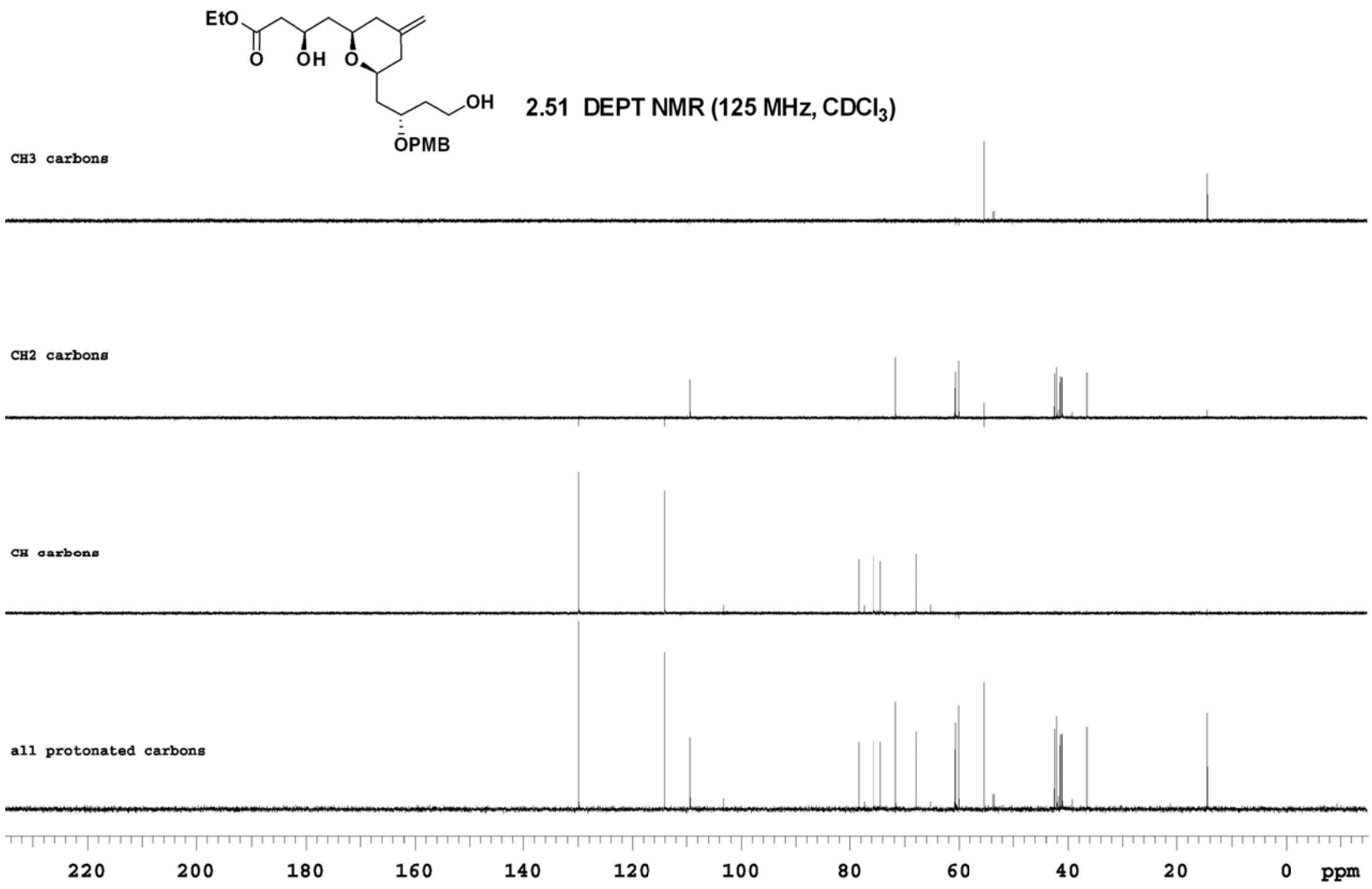

EtO
O
OTBS
O
OTBDPS
OPMB
2.39 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
ppm

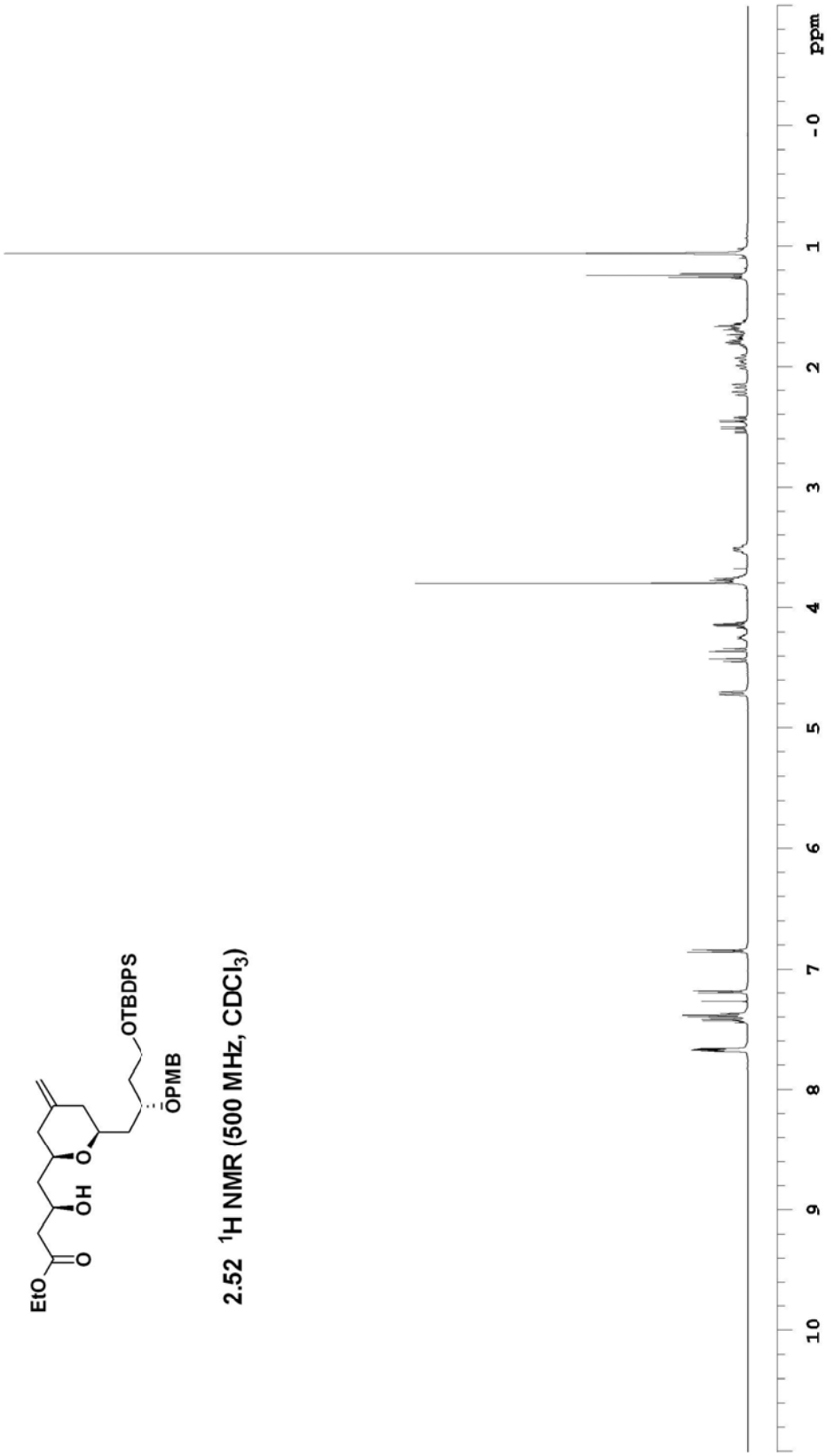


2.51 ^{1}H NMR (500 MHz, $CDCl_3$)

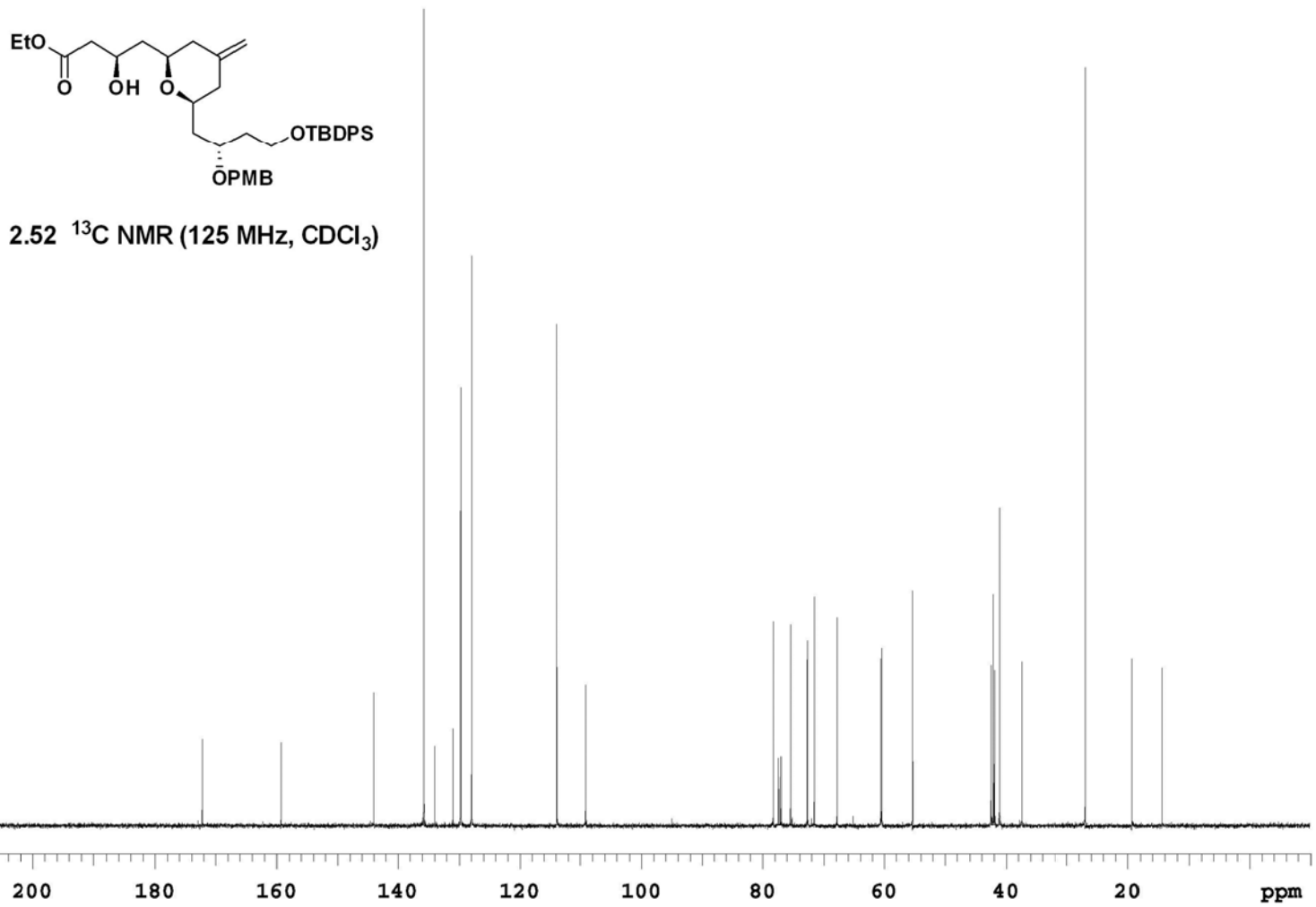


2.51 ^{13}C NMR (125 MHz, $CDCl_3$)

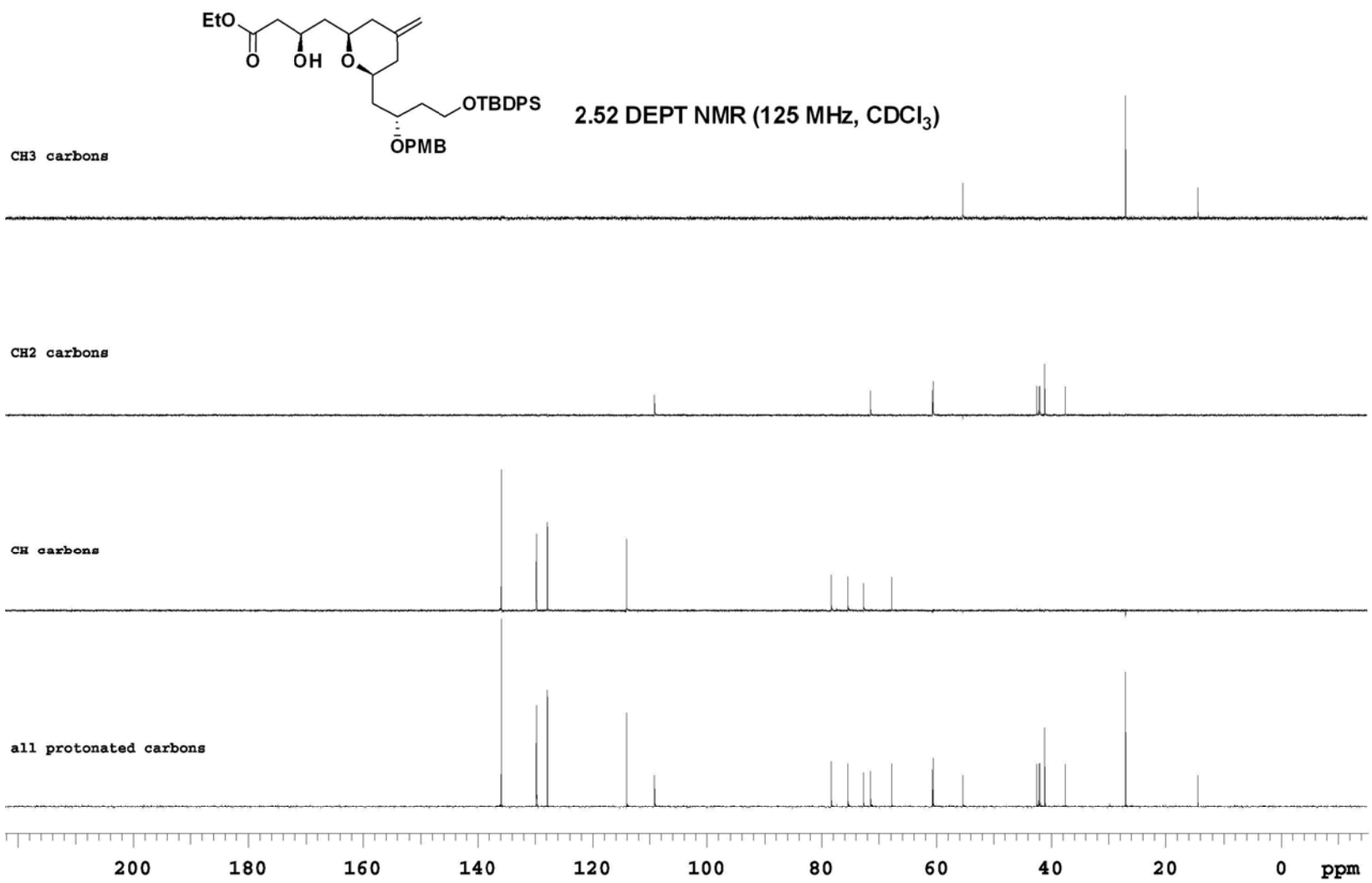

EtO
O
OH
O
OH
OPMB
2.51 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
ppm

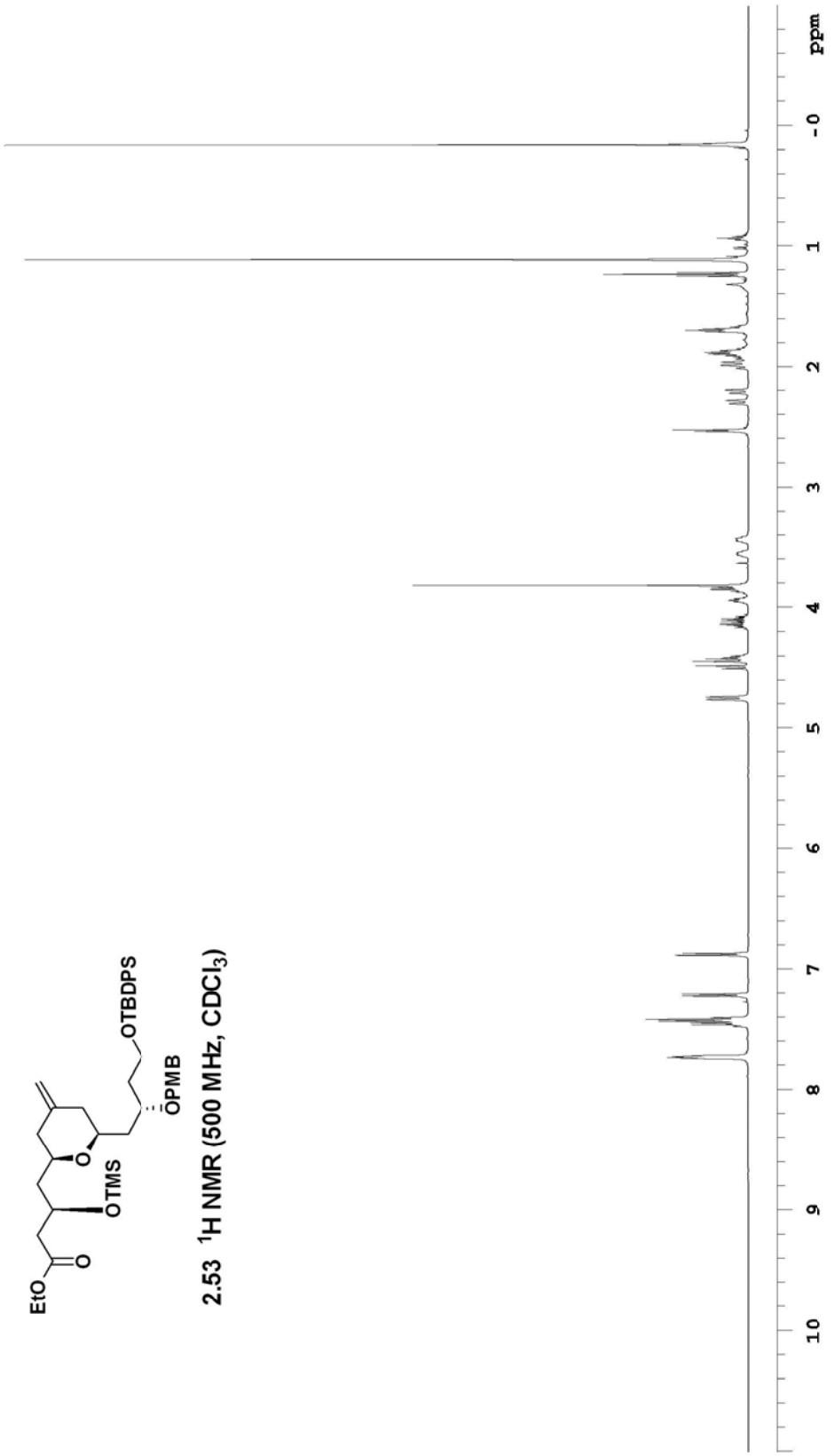


2.52 ^{1}H NMR (500 MHz, $CDCl_3$)

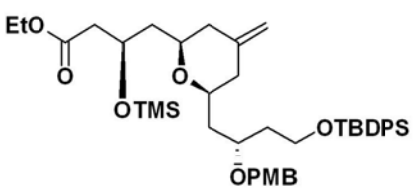


2.52 ^{13}C NMR (125 MHz, $CDCl_3$)

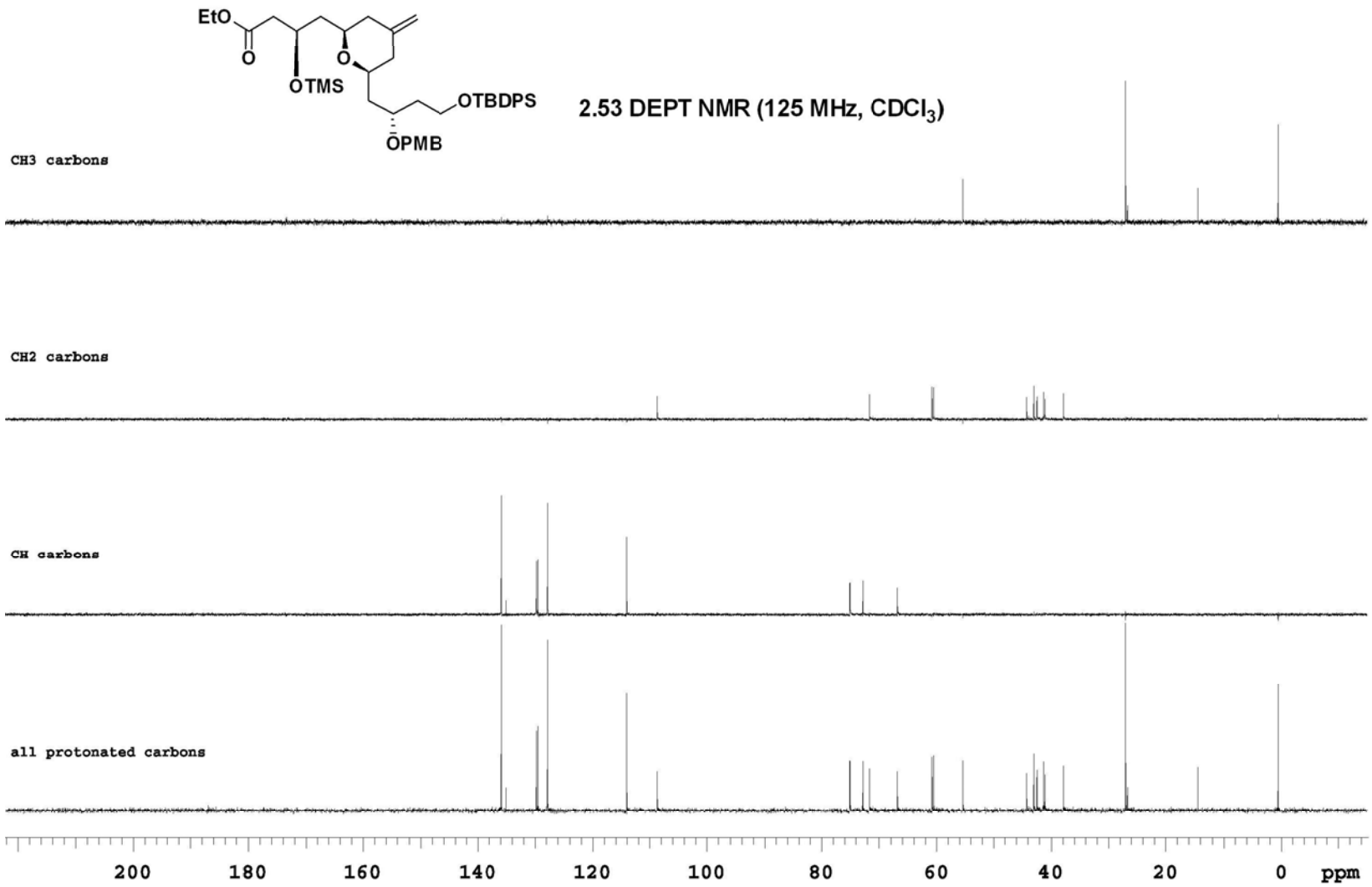

EtO
O
OH
O
OTBDPS
OPMB
2.52 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

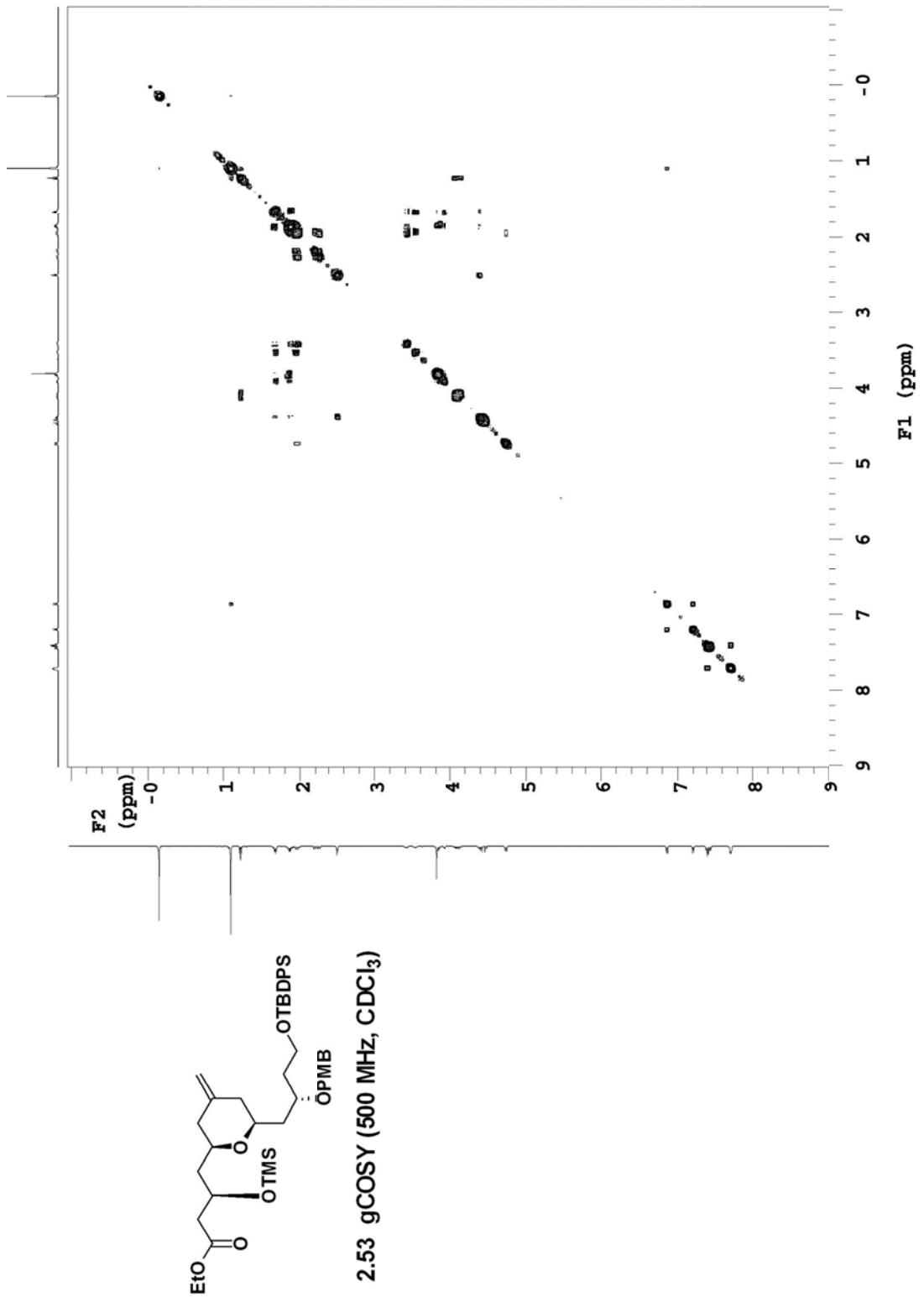


2.53 ^{1}H NMR (500 MHz, $CDCl_3$)

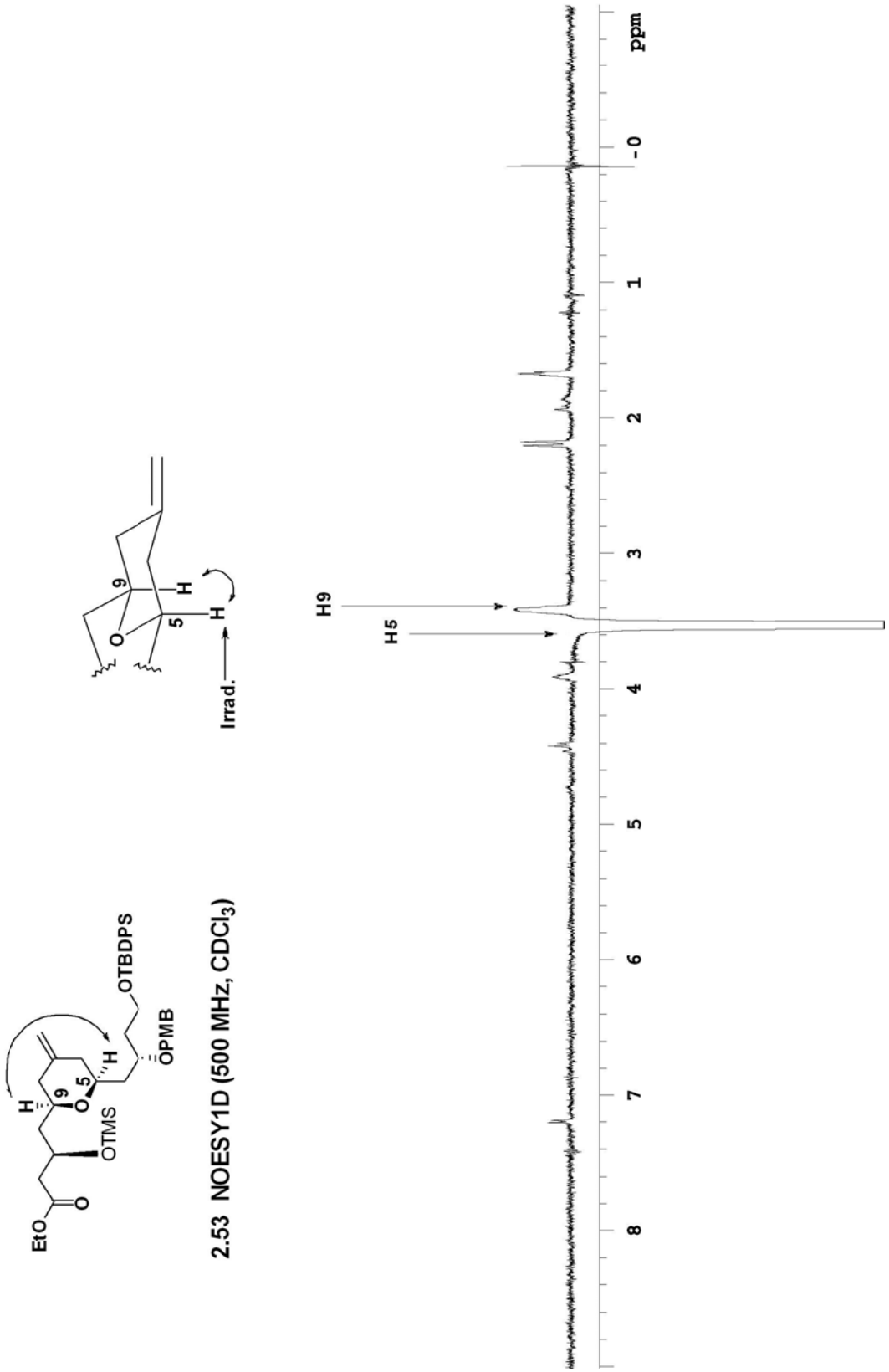


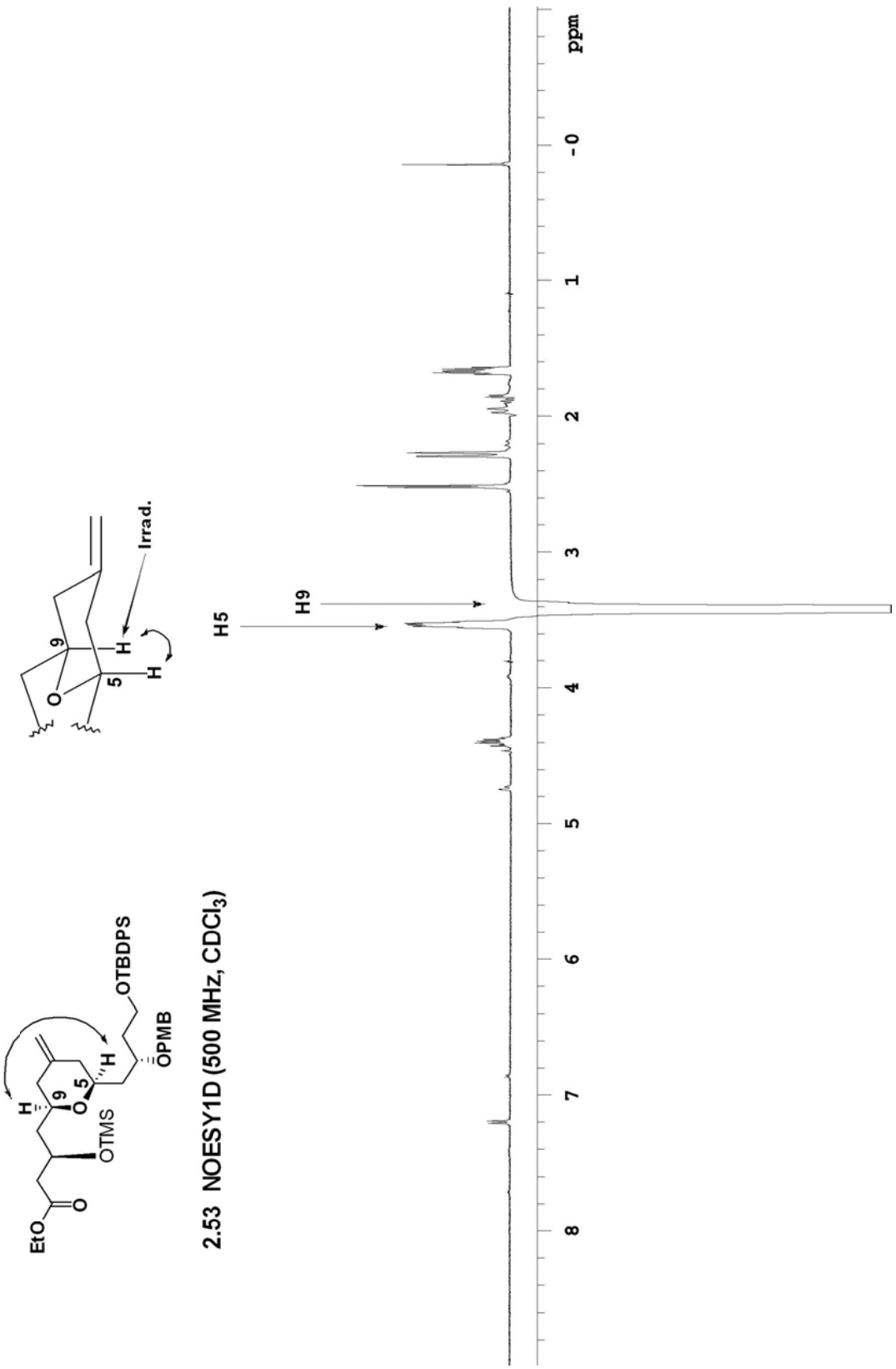
2.53 ^{13}C NMR (125 MHz, $CDCl_3$)


EtO
O
OTMS
O
OTBDPS
OPMB
2.53 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

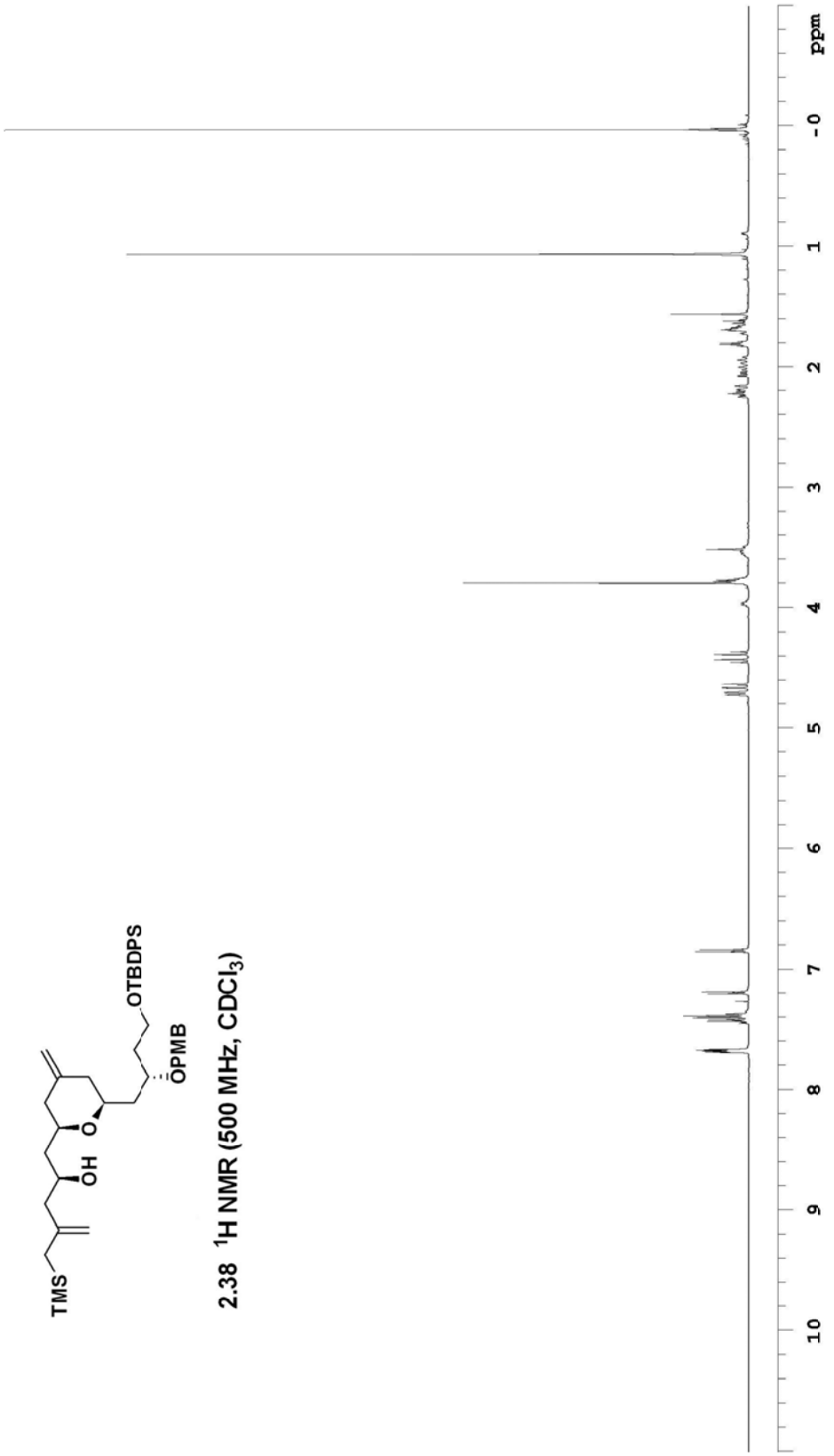


2.53 gCOSY (500 MHz, $CDCl_3$)

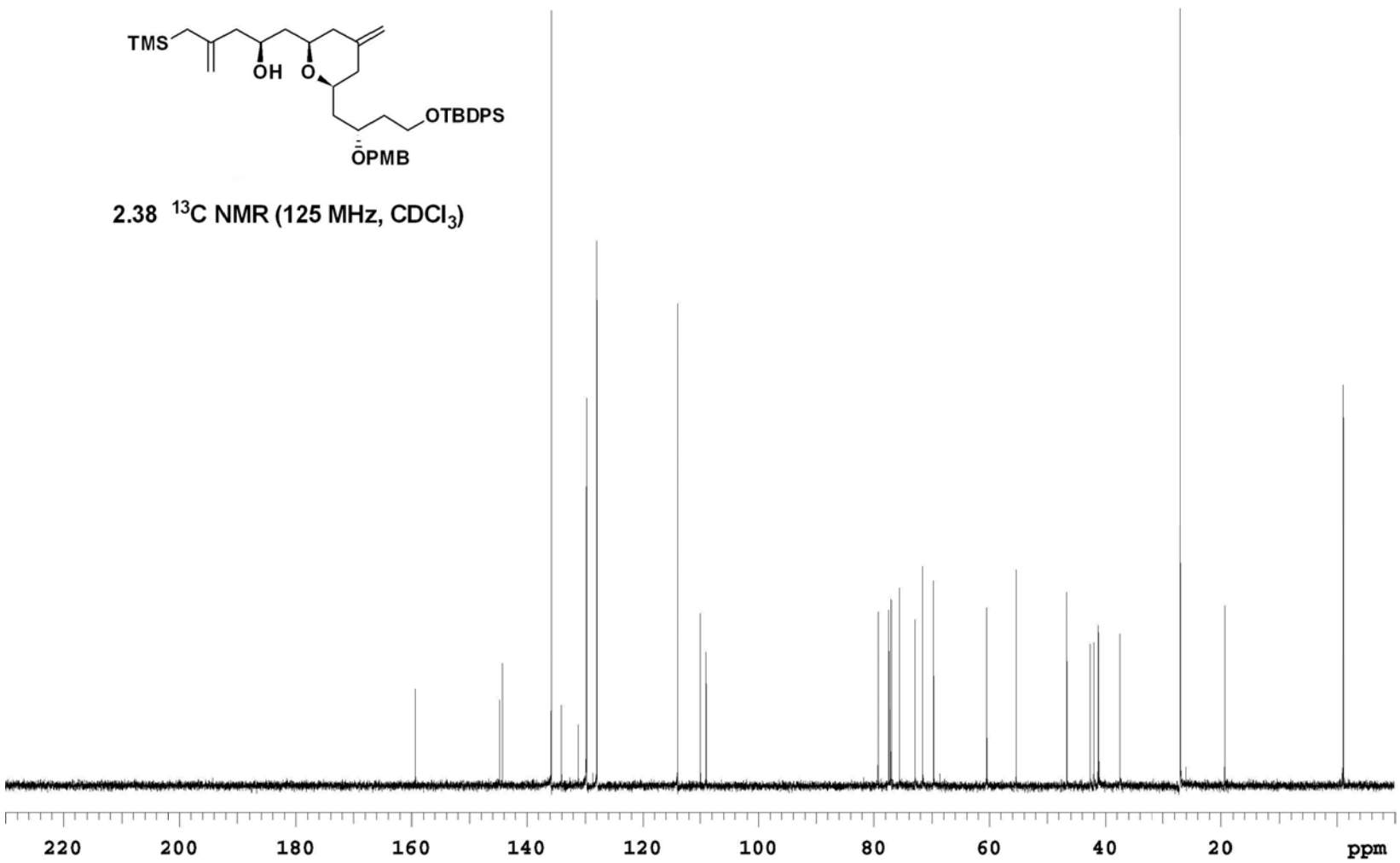

EtO
O
OTMS
H
9
O
5
H
OTBDPS
OPMB
2.53 NOESY1D (500 MHz, CDCl3)
9
H
5
O
H
H
Irrad.
H9
H5
ppm
-0
1
2
3
4
5
6
7
8



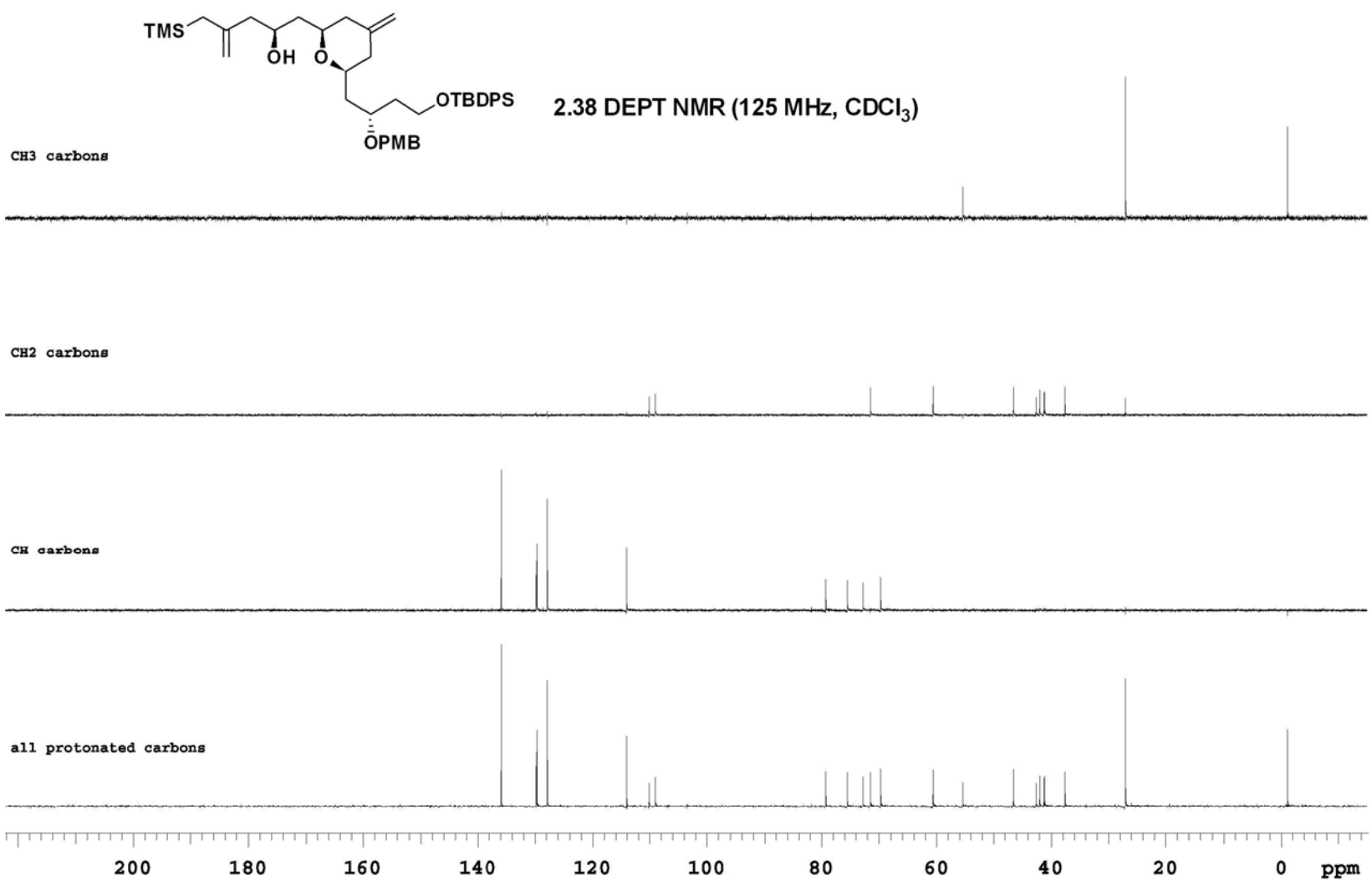
2.53 NOESY1D (500 MHz, $CDCl_3$)

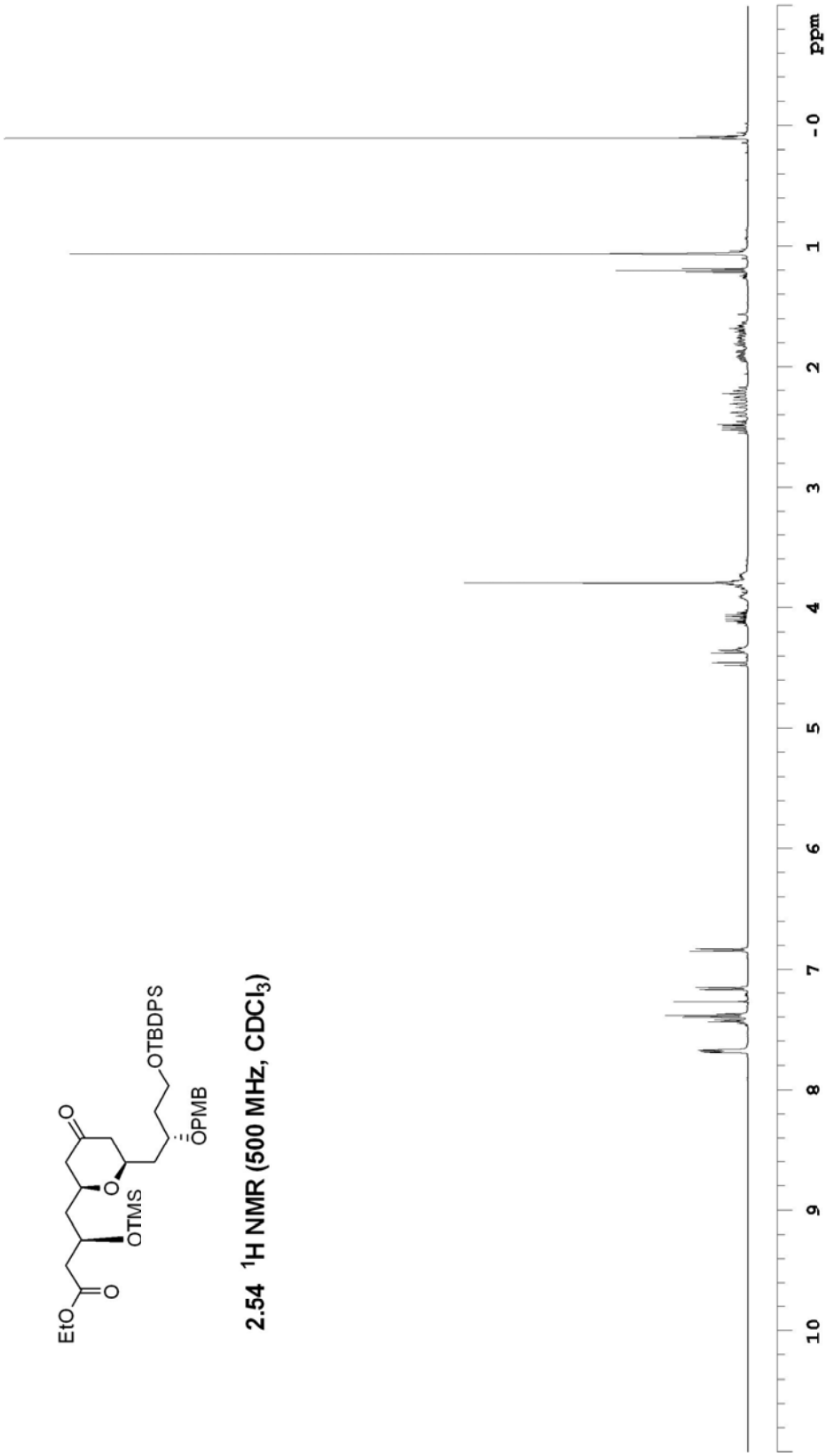


2.38 ^{1}H NMR (500 MHz, $CDCl_3$)

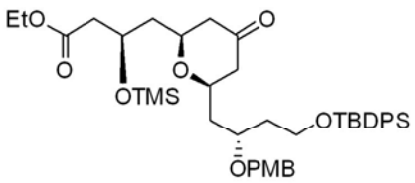


2.38 ^{13}C NMR (125 MHz, $CDCl_3$)

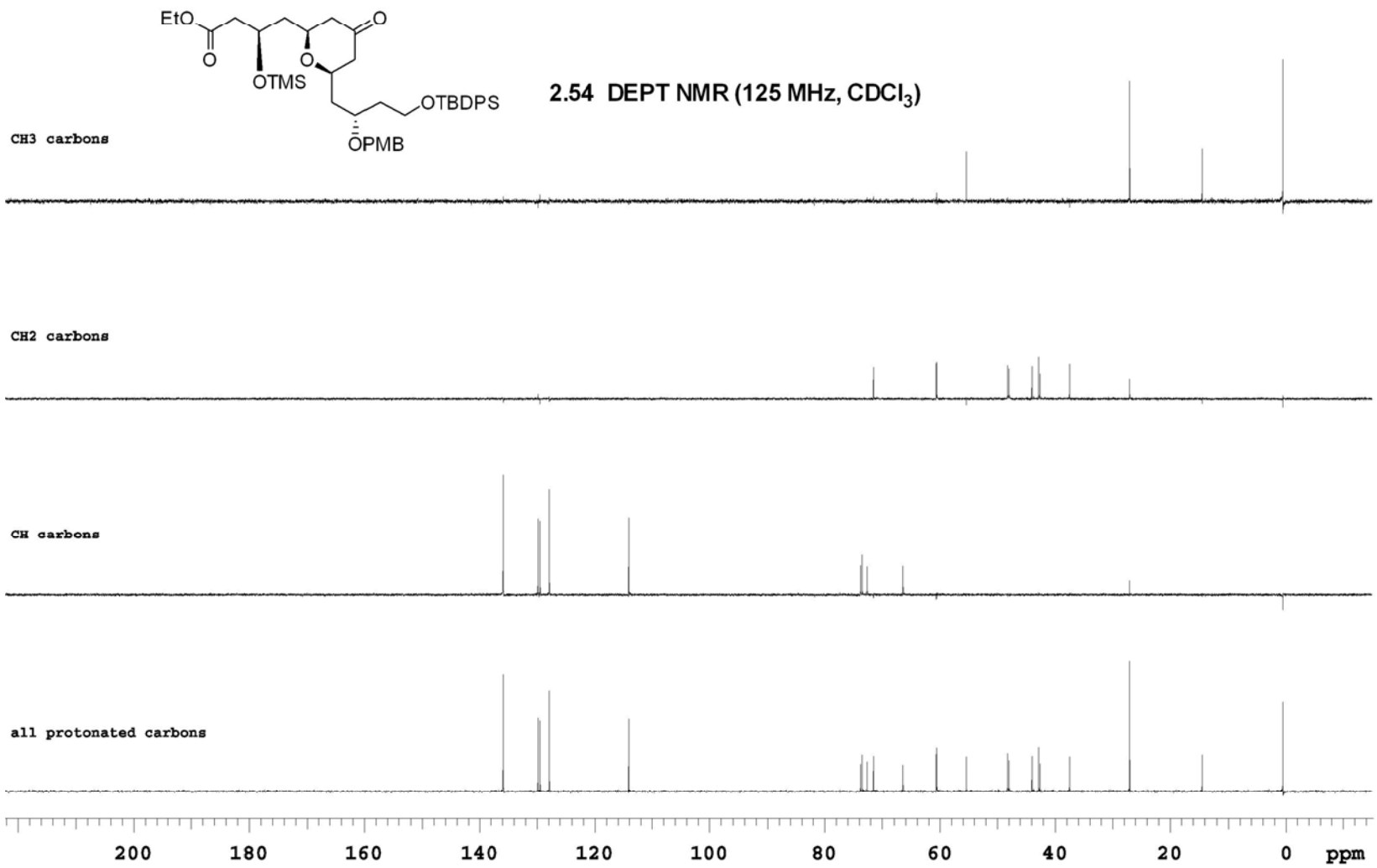

TMS
OH
O
OTBDPS
OPMB
2.38 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

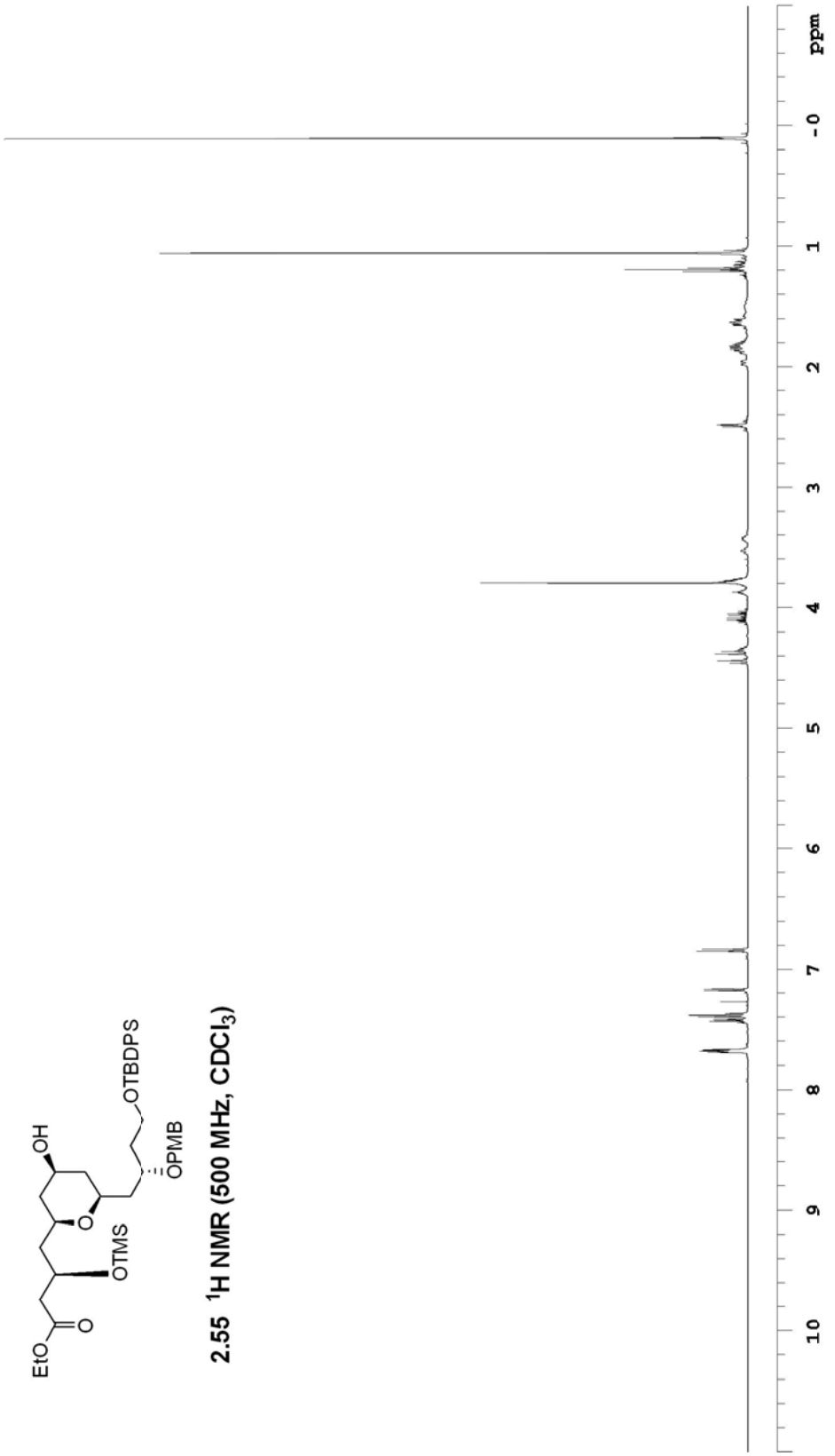


2.54 ^{1}H NMR (500 MHz, $CDCl_3$)

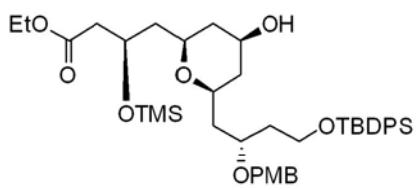


2.54 ^{13}C **NMR (125 MHz,** $CDCl_3$**)**

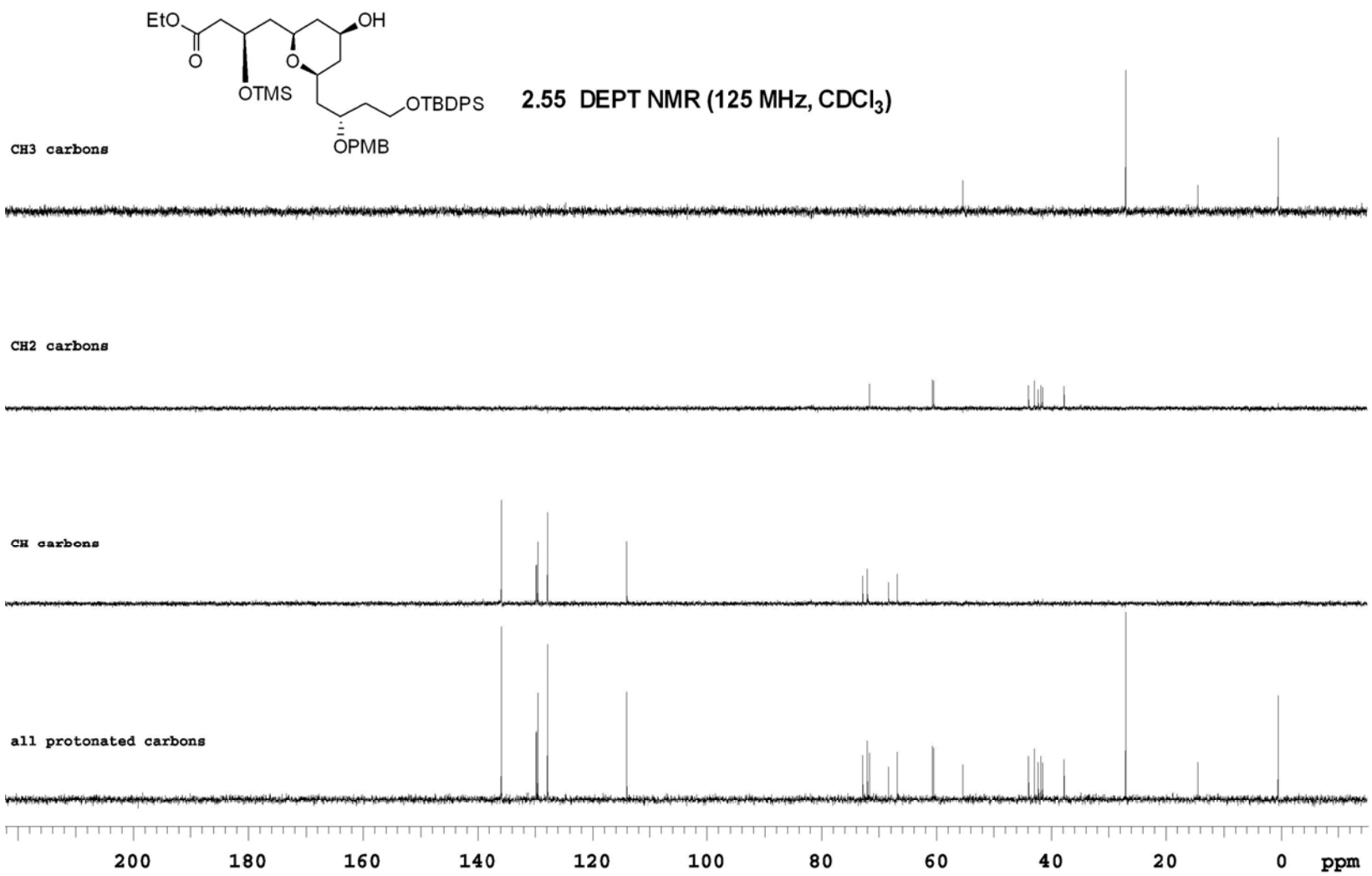

EtO
O
O
OTMS
O
O
OTBDPS
OPMB
2.54 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

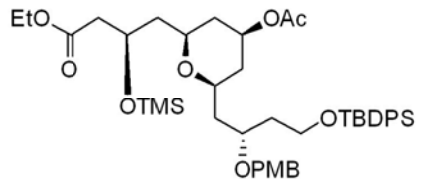


2.55 ^{1}H NMR (500 MHz, $CDCl_3$)

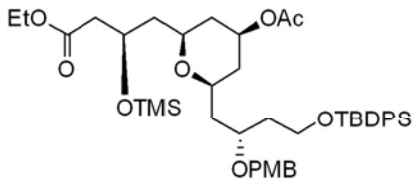


2.55 ^{13}C NMR (125 MHz, $CDCl_3$)

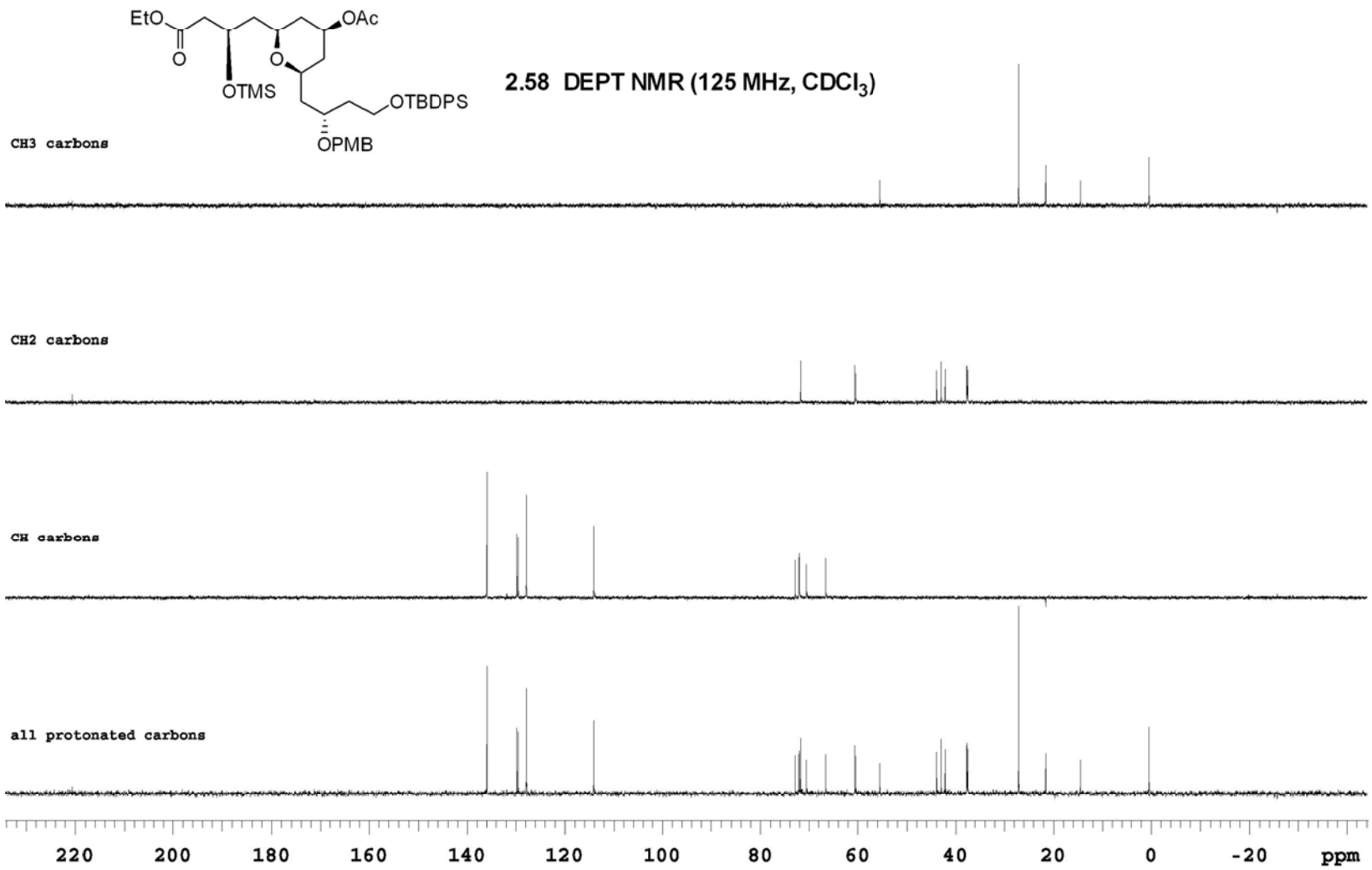

EtO
O
OTMS
O
OH
OTBDPS
OPMB
2.55 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

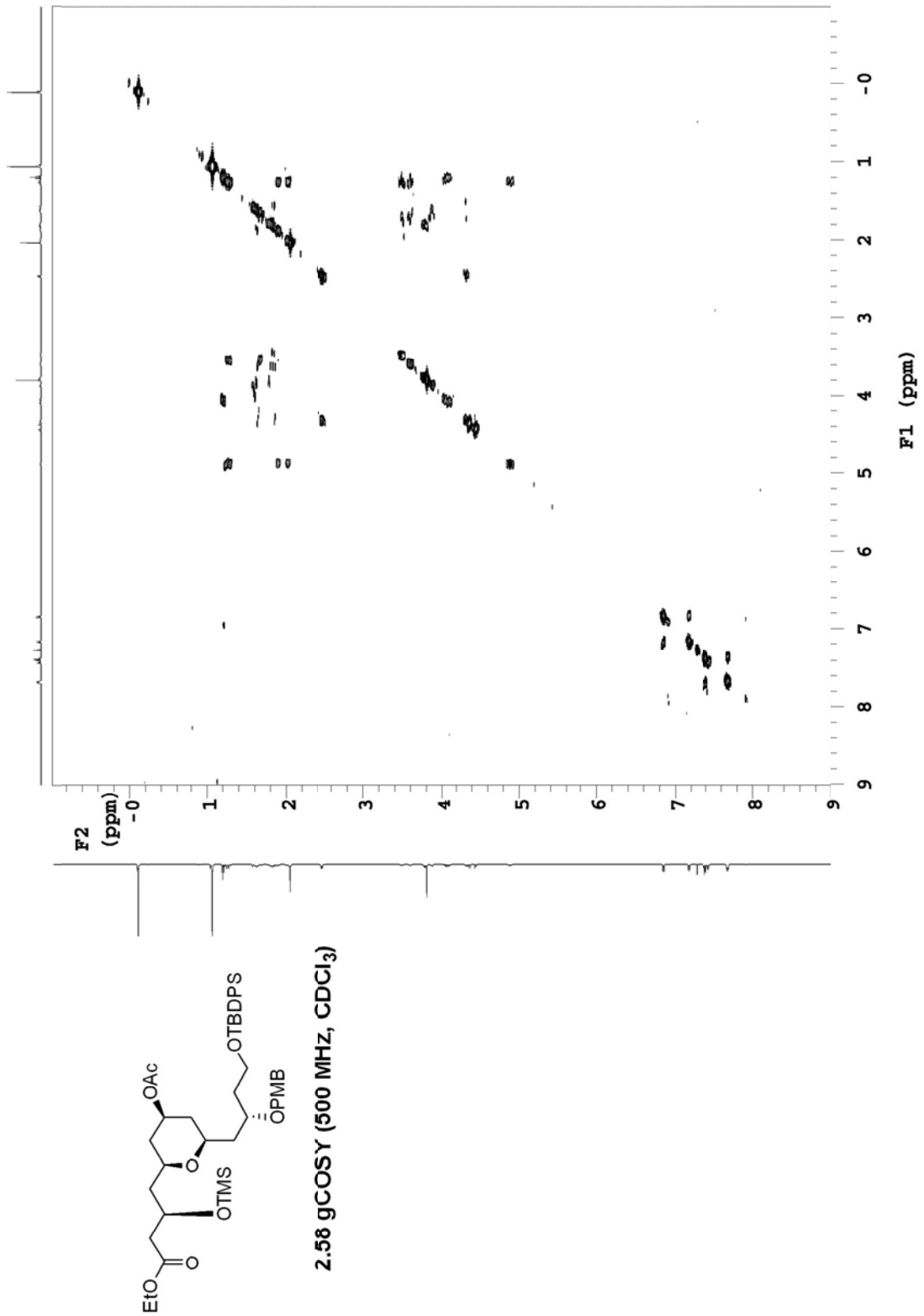


2.58 ^{1}H NMR (500 MHz, $CDCl_3$)

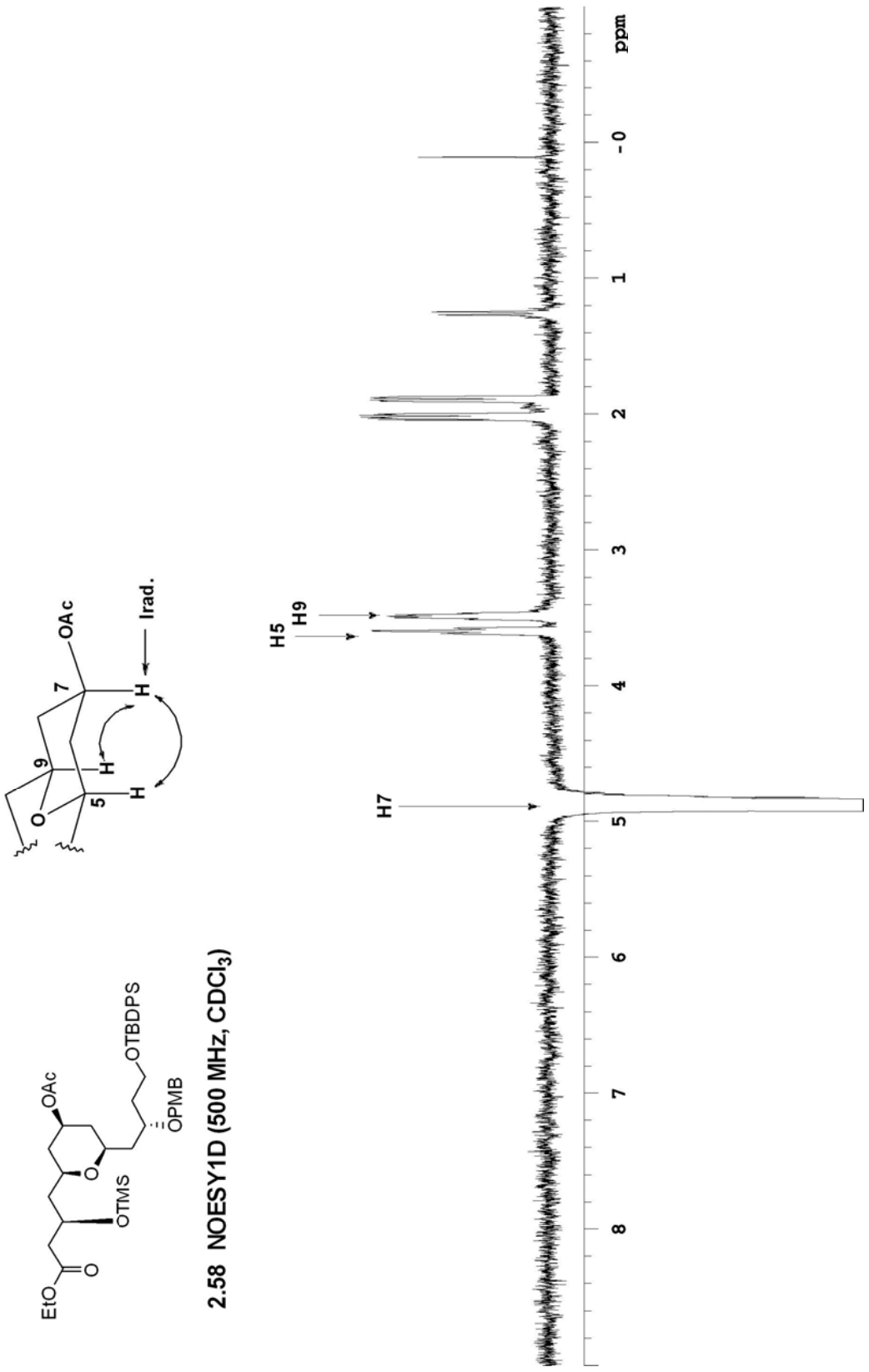


2.58 ^{13}C NMR (125 MHz, $CDCl_3$)

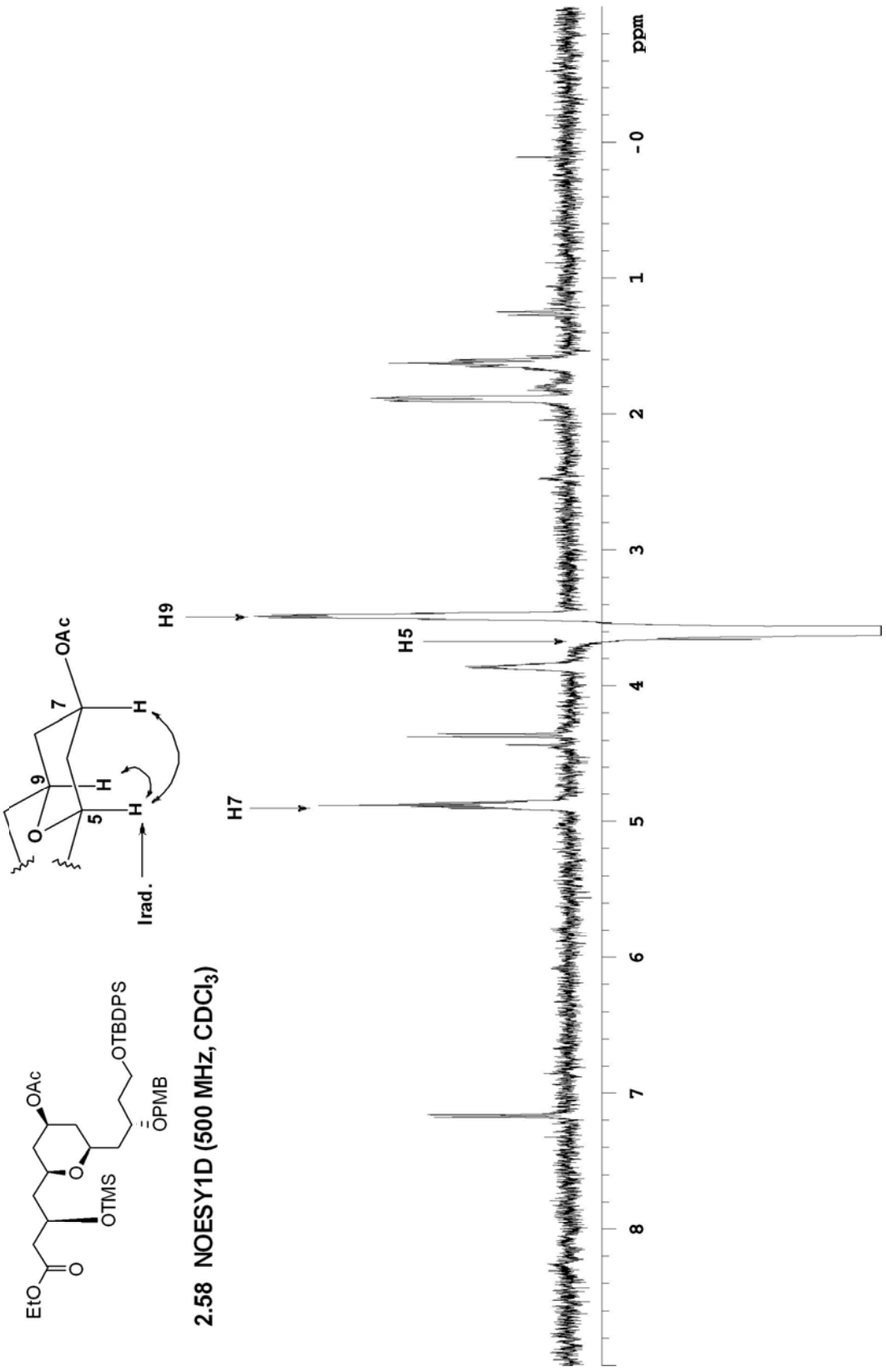

EtO
O
OTMS
O
OAc
OTBDPS
OPMB
2.58 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



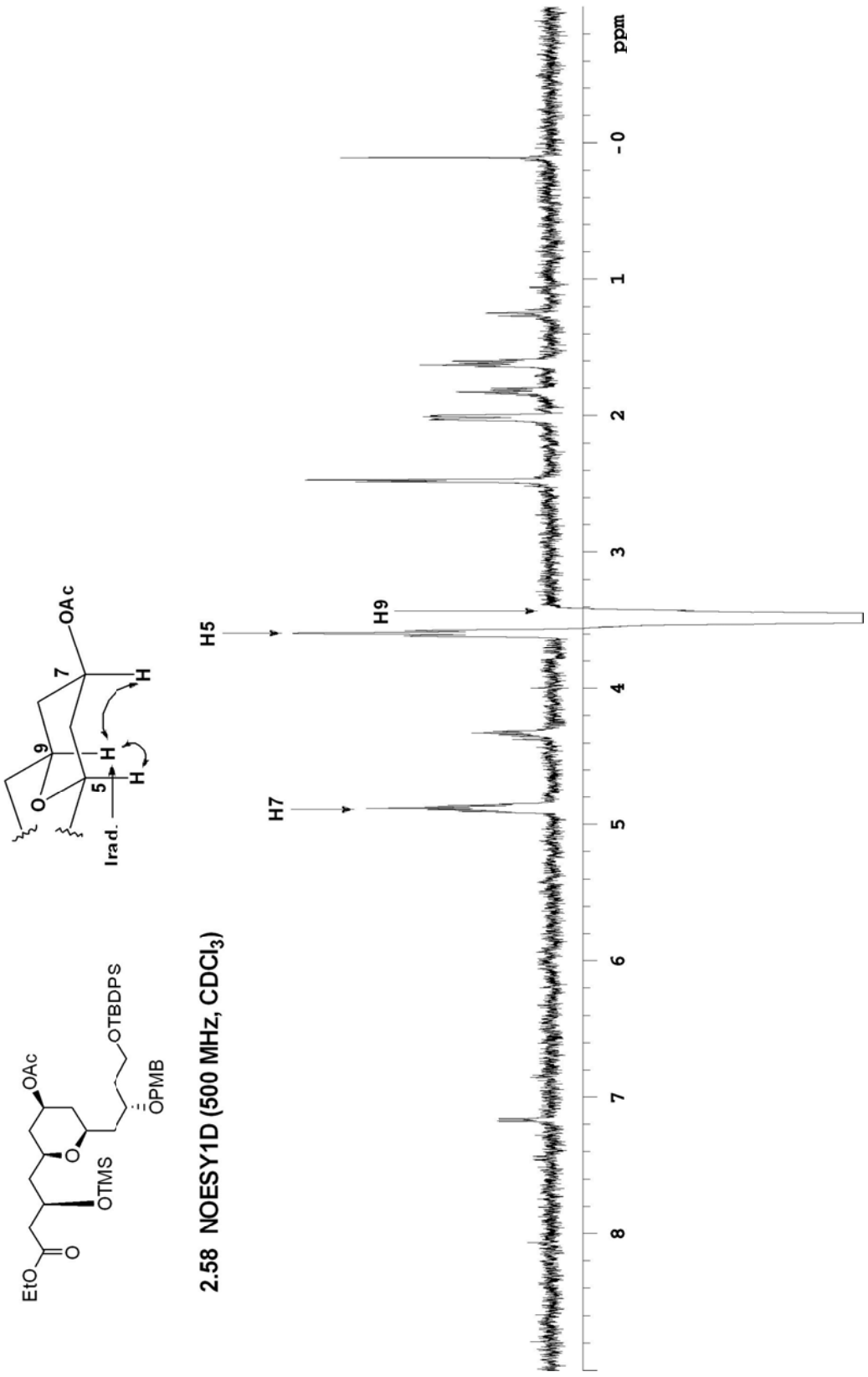
2.58 gCOSY (500 MHz, $CDCl_3$)



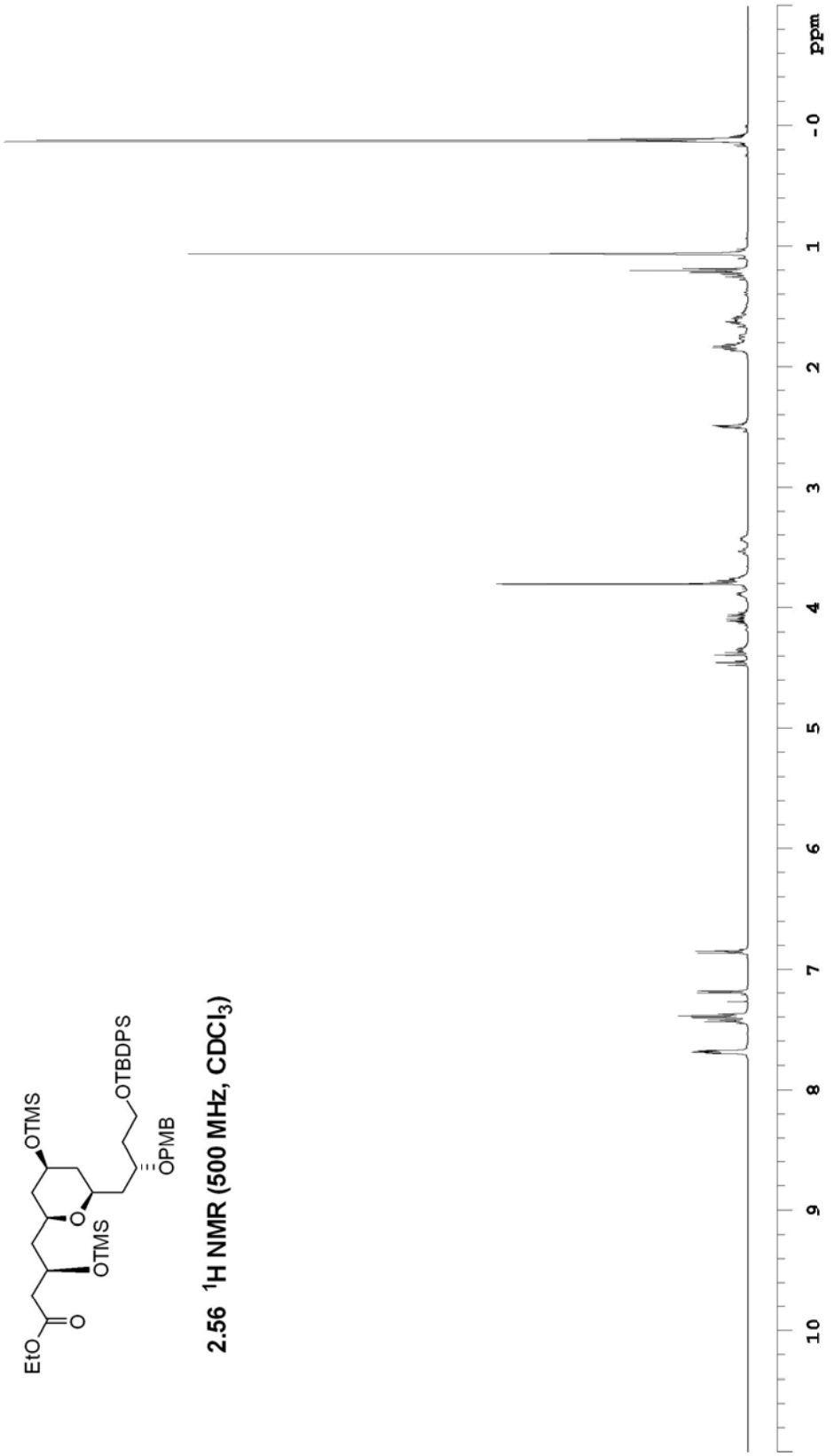
2.58 NOESY1D (500 MHz, $CDCl_3$)



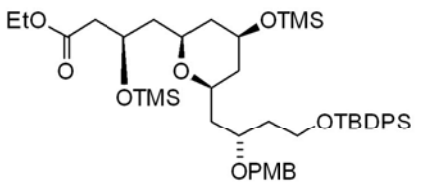
2.58 NOESY1D (500 MHz, $CDCl_3$)



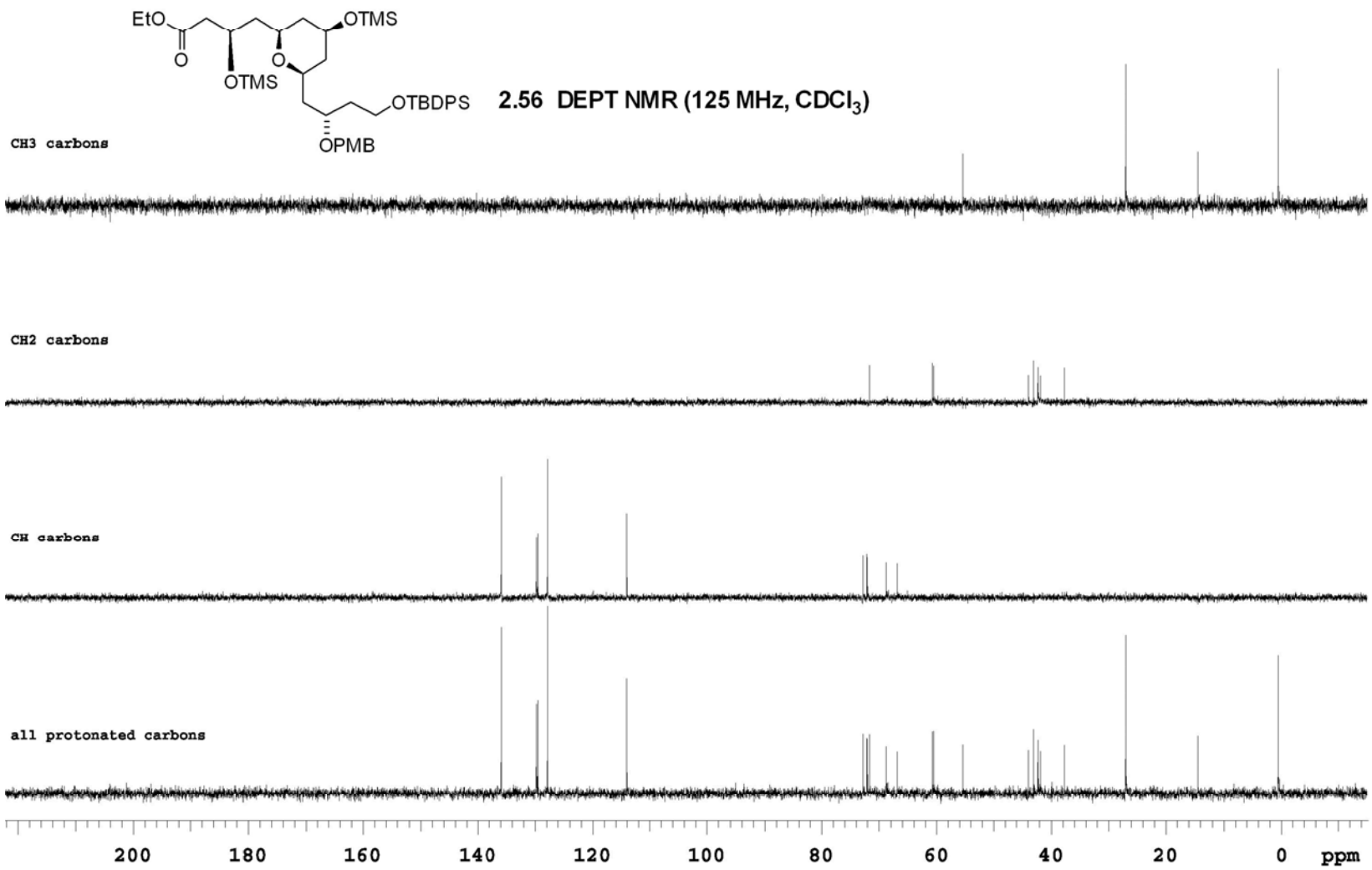
2.58 NOESY1D (500 MHz, $CDCl_3$)

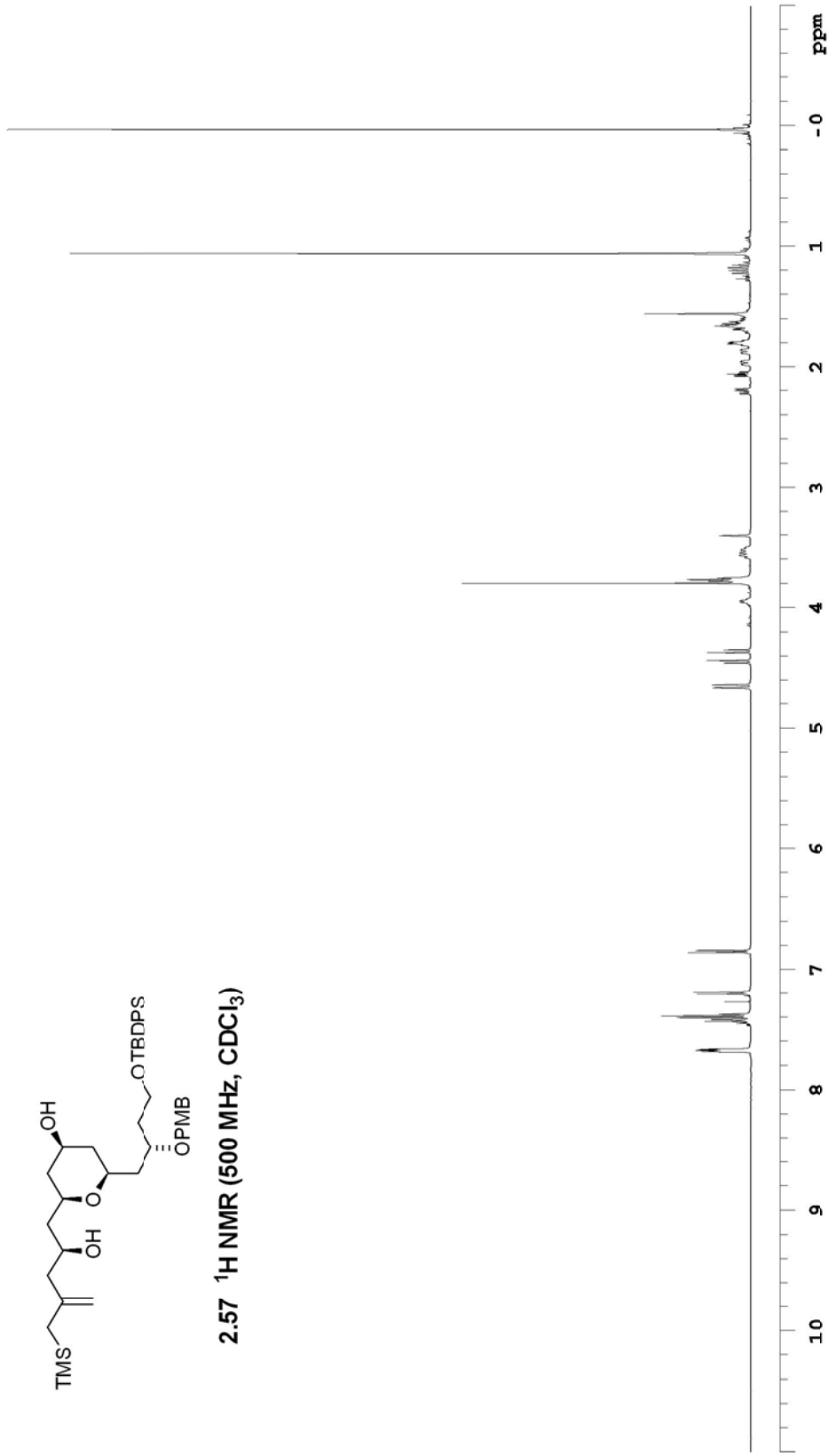


2.56 ^{1}H NMR (500 MHz, $CDCl_3$)

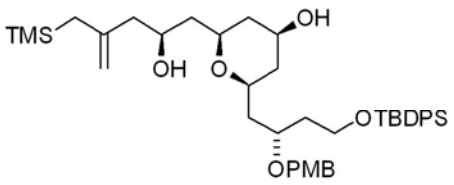


2.56 ^{13}C NMR (125 MHz, $CDCl_3$)

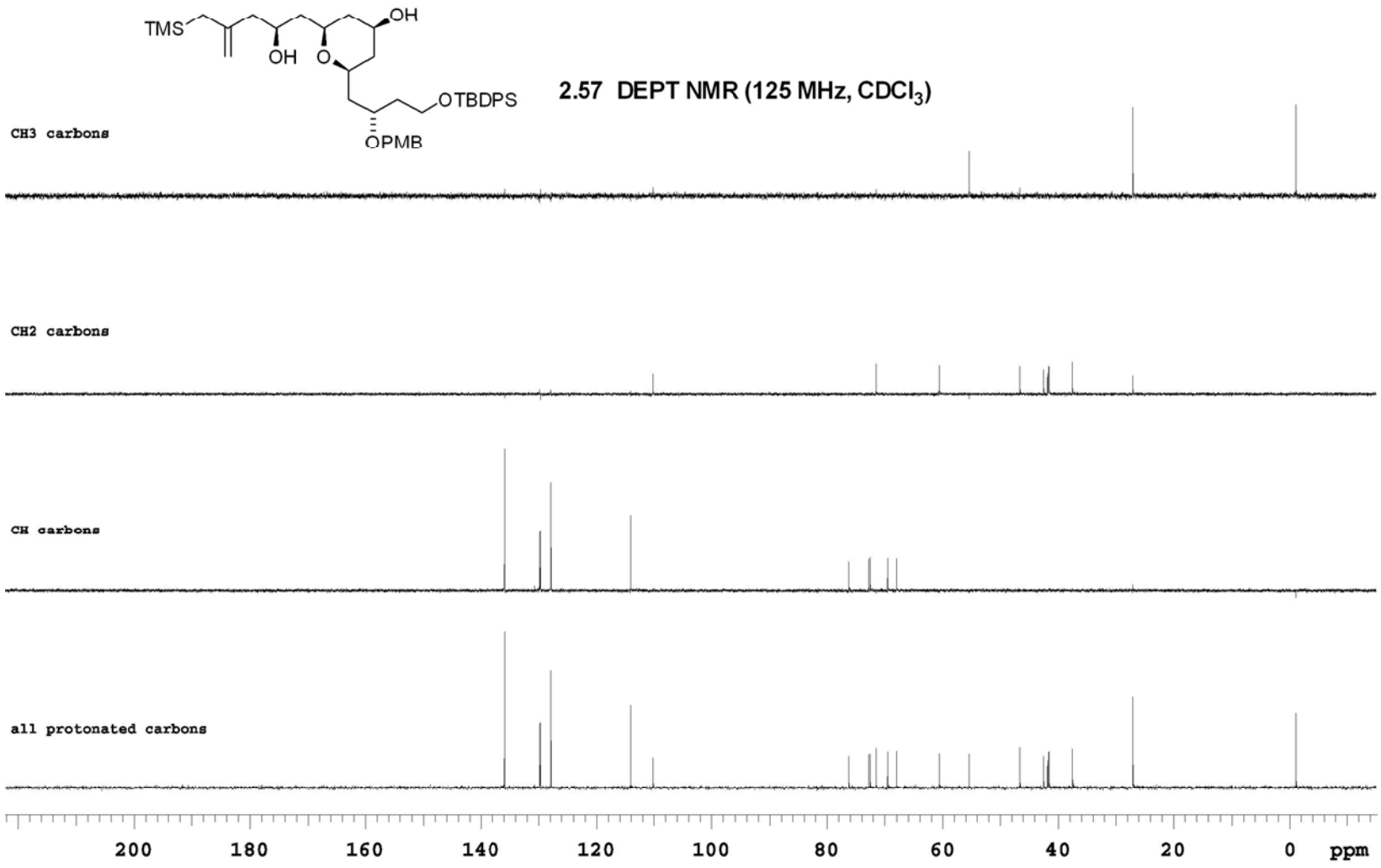

EtO
O
OTMS
O
OTMS
OTBDPS
OPMB
2.56 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

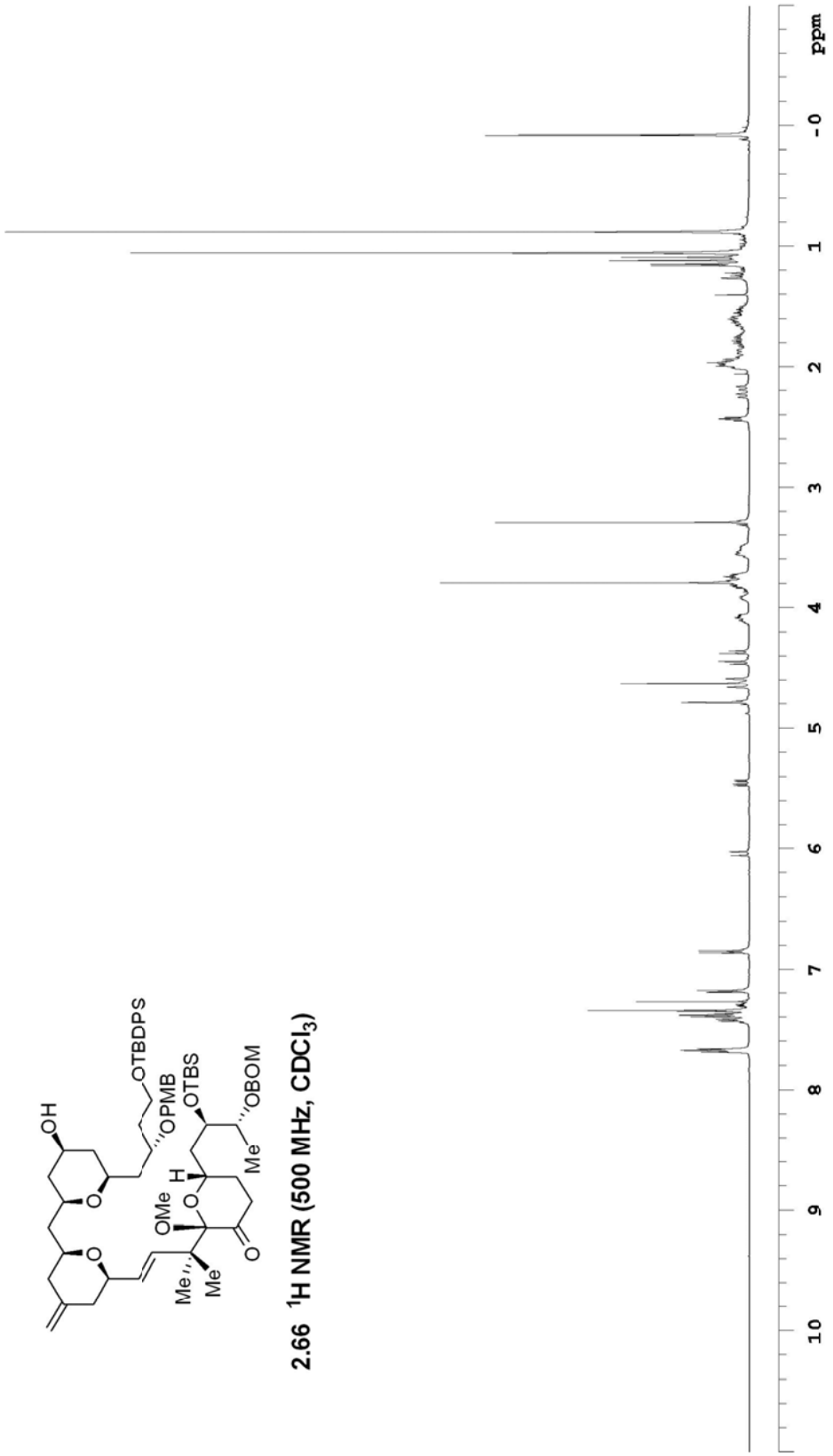


2.57 ^{1}H NMR (500 MHz, $CDCl_3$)

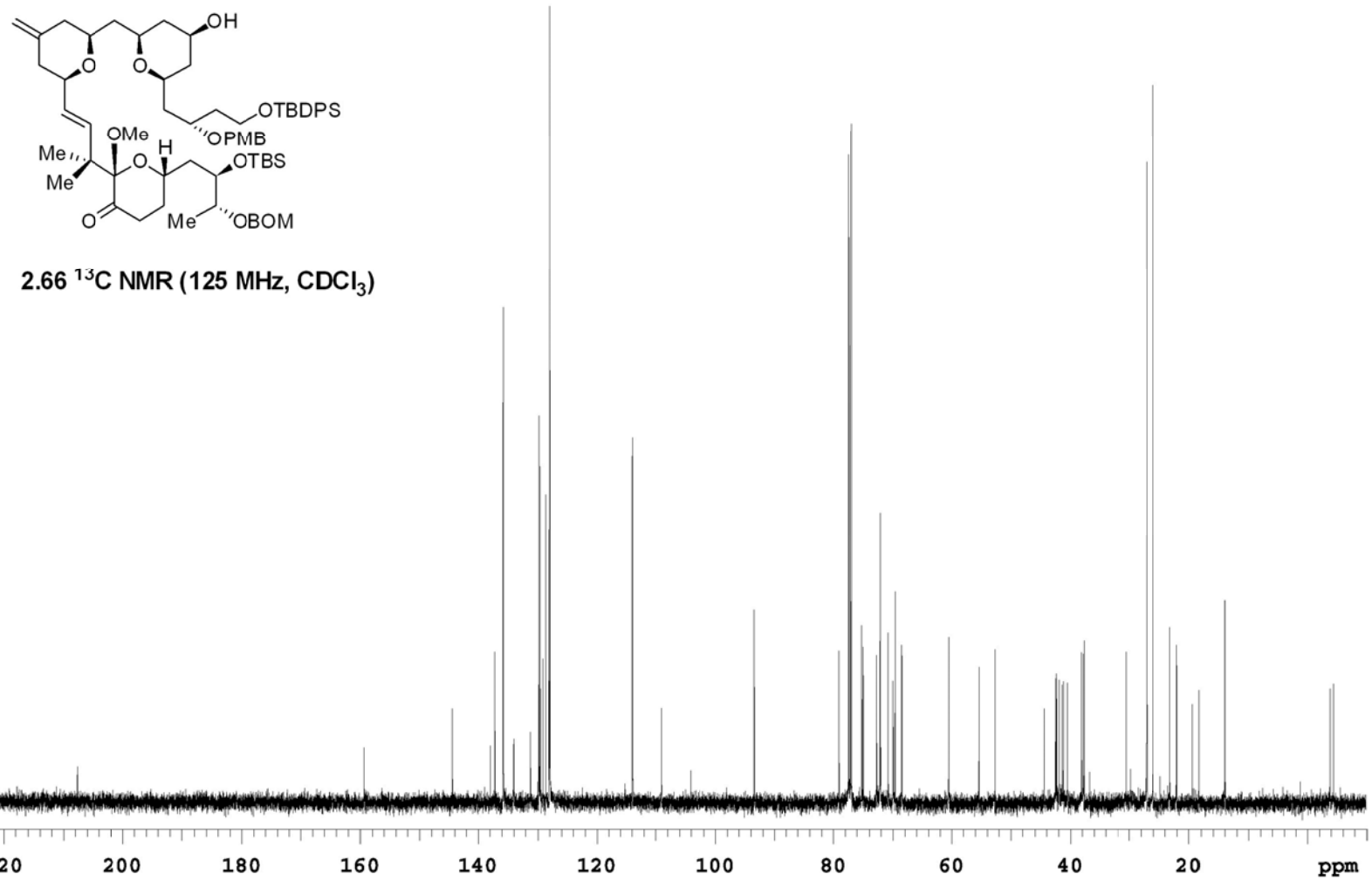


2.57 ^{13}C NMR (125 MHz, $CDCl_3$)

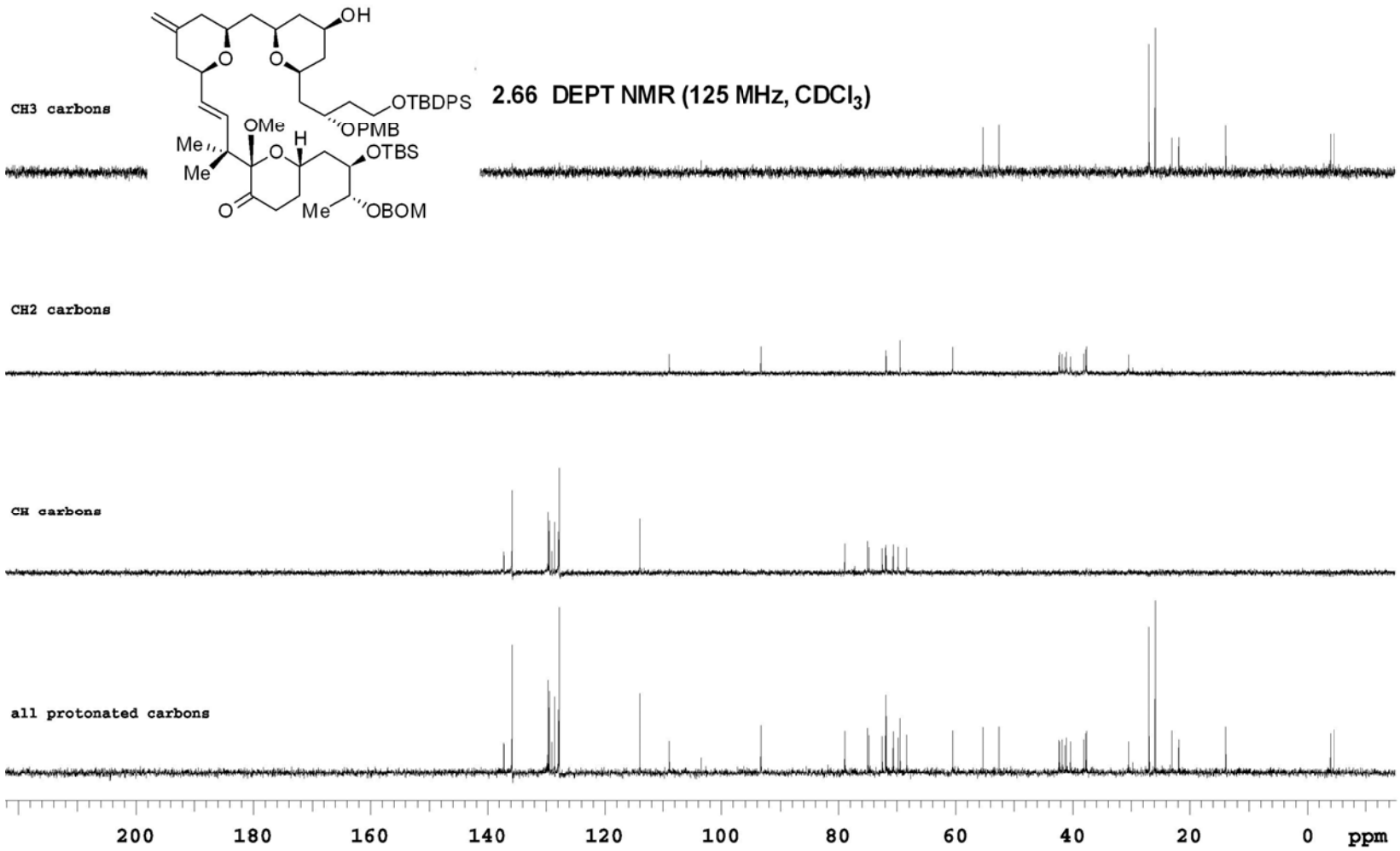

TMS
OH
OH
O
OTBDPS
OPMB
2.57 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

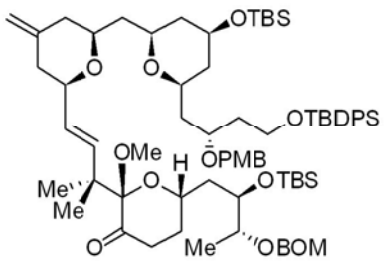


2.66 ^{1}H NMR (500 MHz, $CDCl_3$)

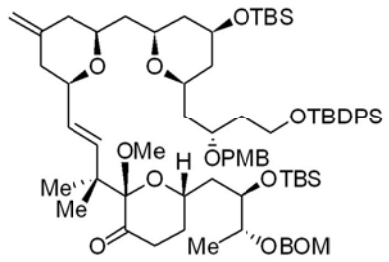


2.66 ^{13}C NMR (125 MHz, $CDCl_3$)

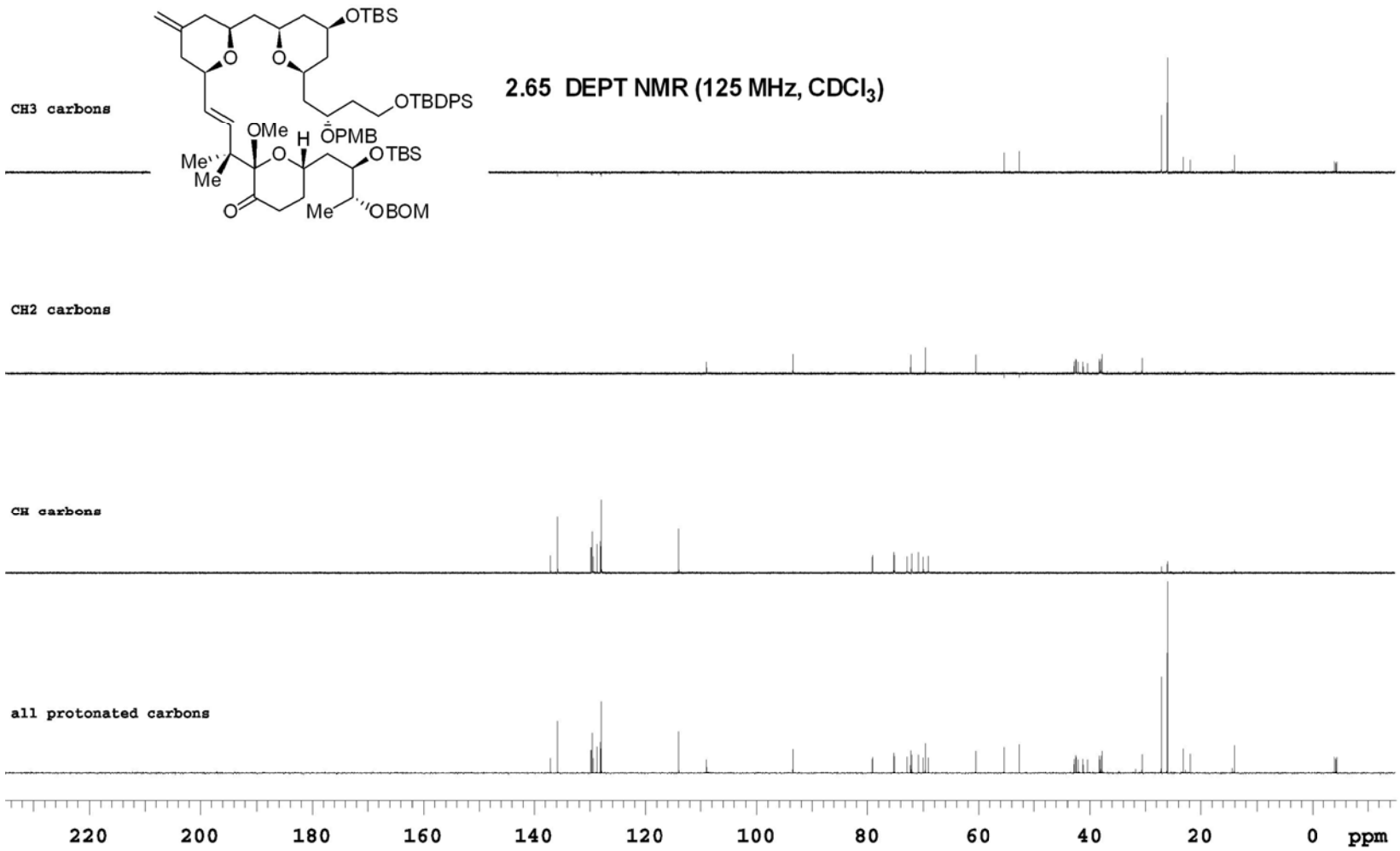

OH
OTBDPS
OPMB
OMe
H
Me
Me
OTBS
Me
OBOM
2.66 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

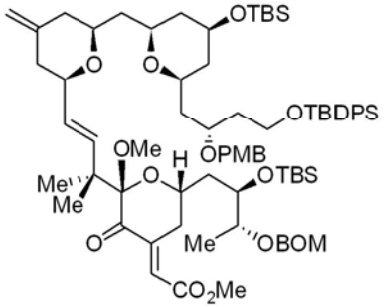


2.65 ^{1}H NMR (500 MHz, $CDCl_3$)

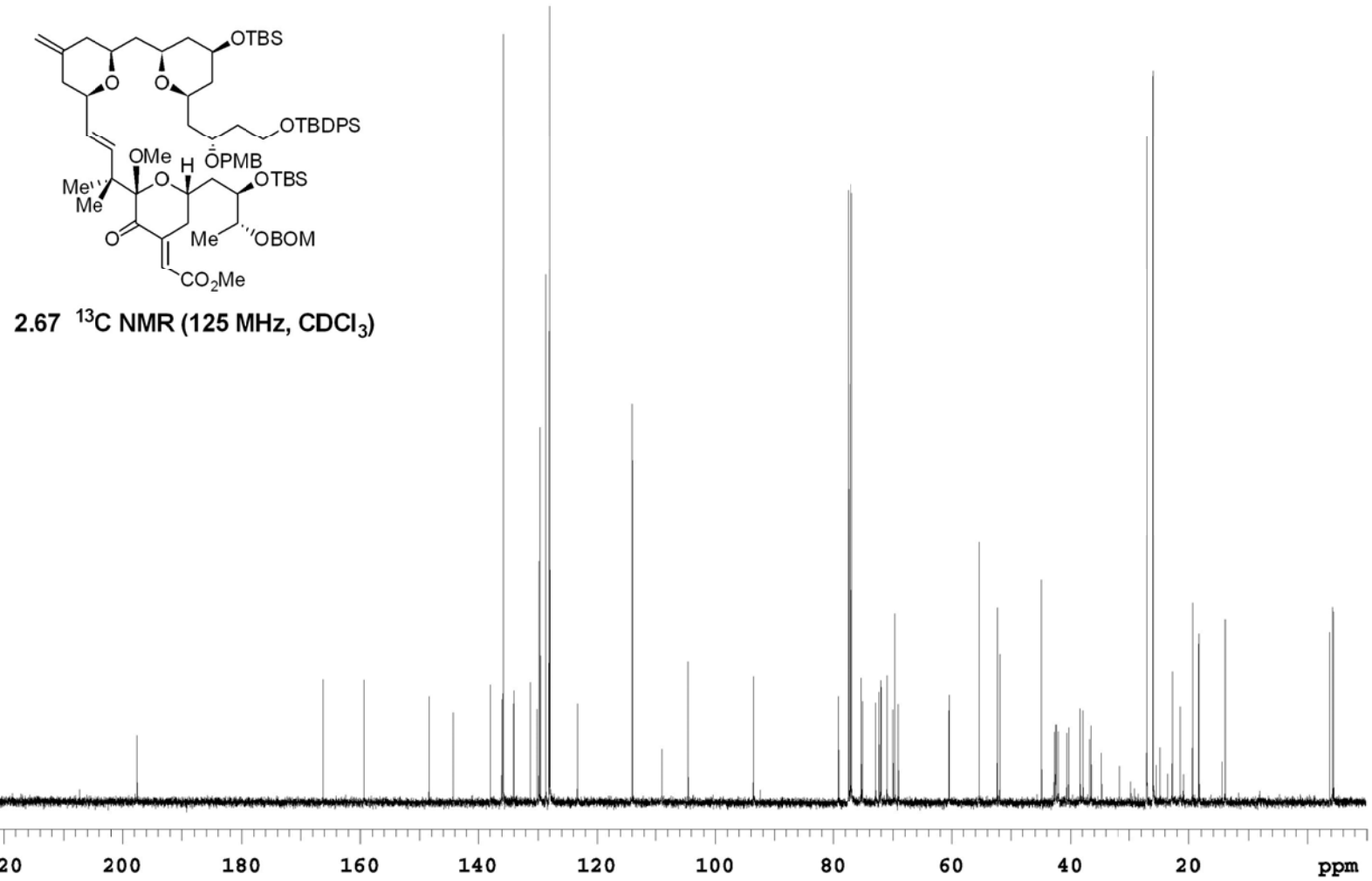


2.65 ^{13}C NMR (125 MHz, $CDCl_3$)

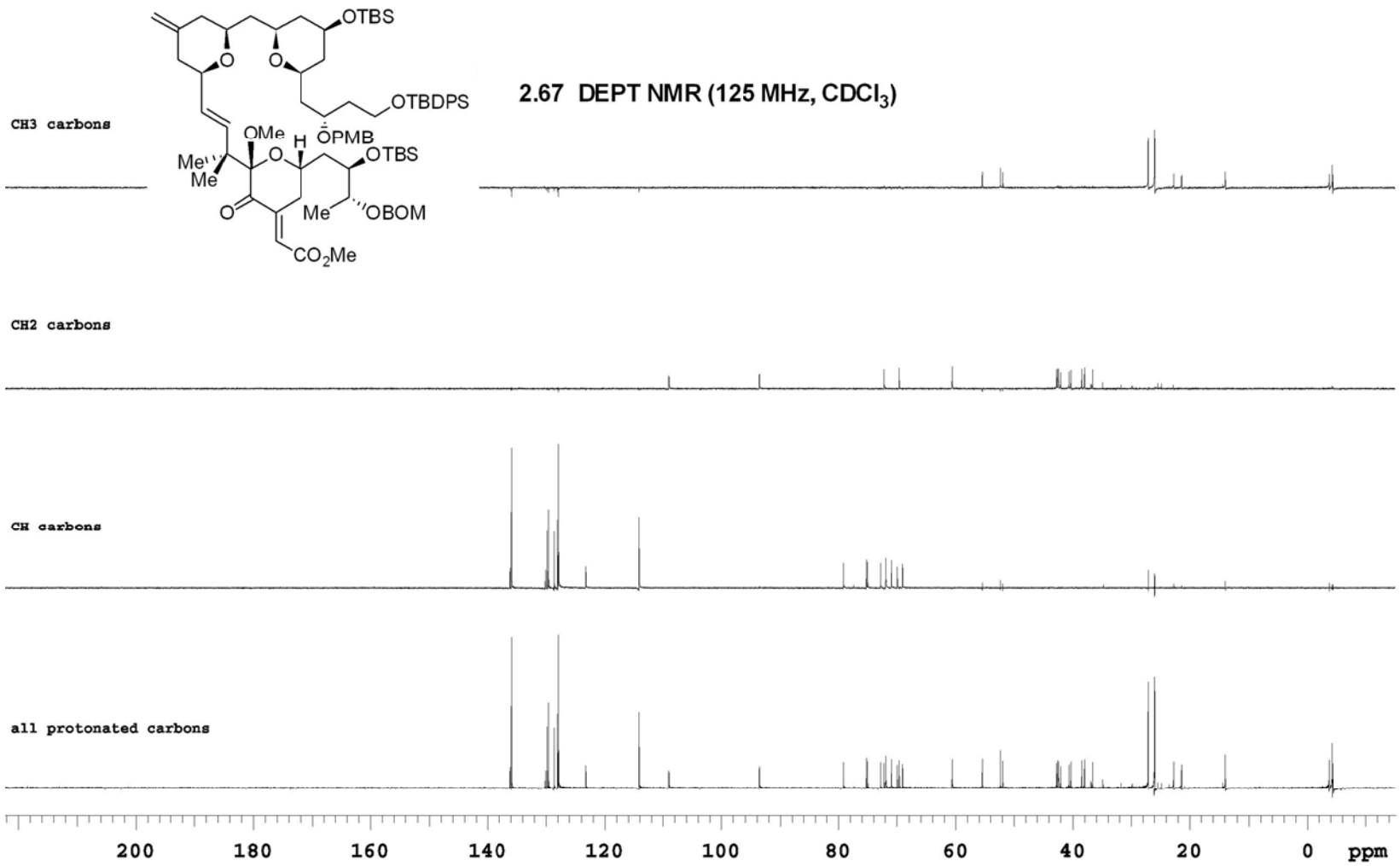

OTBS
OTBDPS
OMe
H
OPMB
OTBS
Me
Me
Me
OBOM
O
2.65 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
ppm

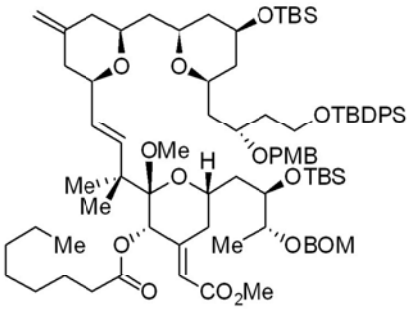


2.67 ^{1}H NMR (500 MHz, $CDCl_3$)

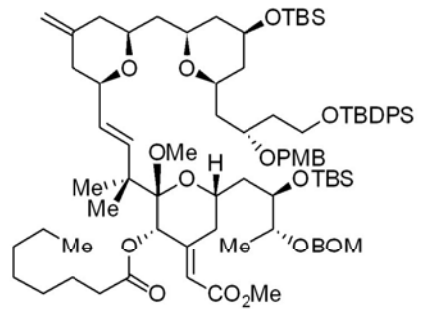


2.67 ^{13}C NMR (125 MHz, $CDCl_3$)

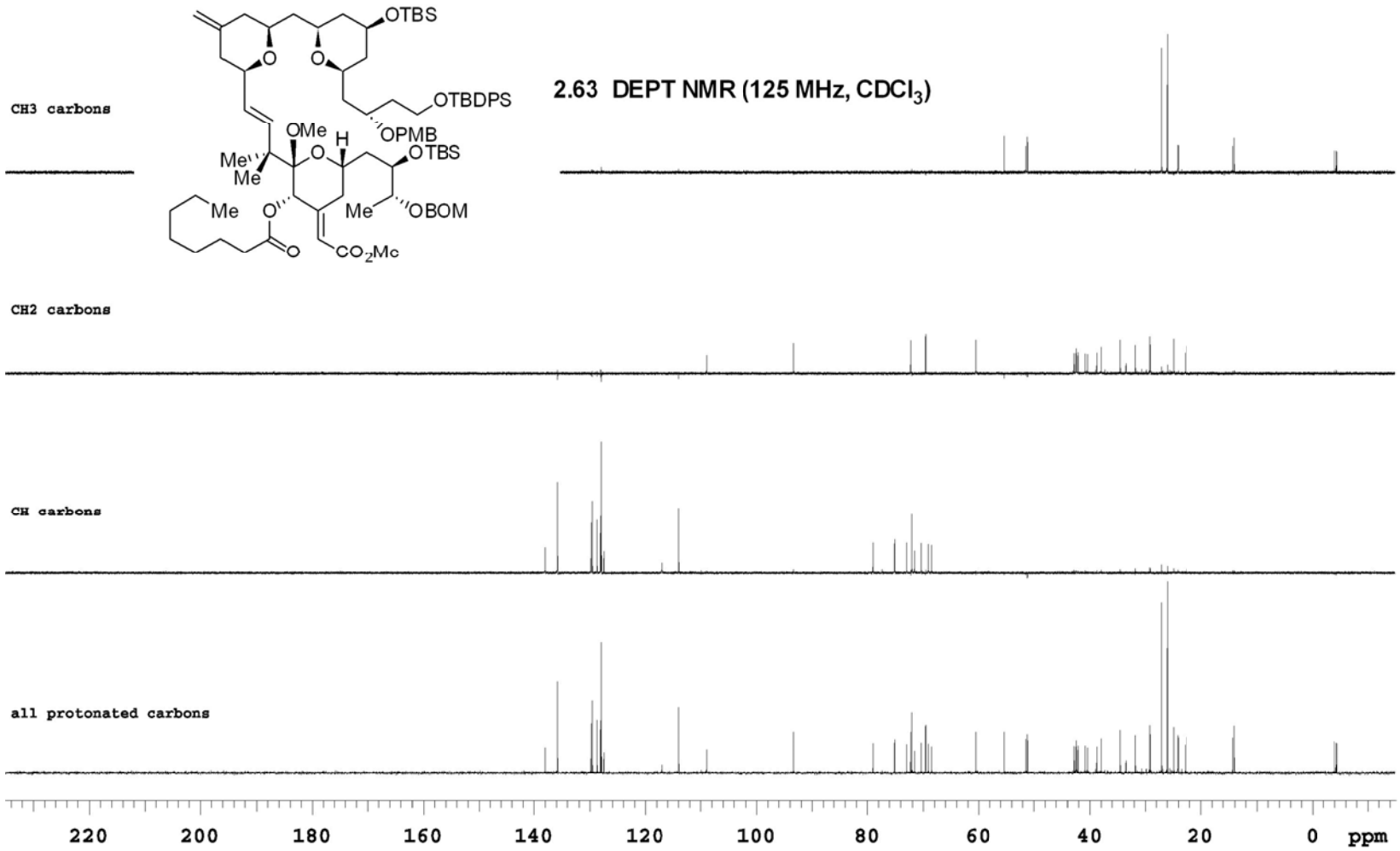

OTBS
OTBDPS
OMe
H
OPMB
OTBS
Me
Me
O
Me
OBOM
CO2Me
2.67 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

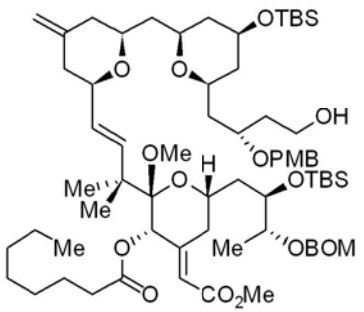


2.63 ^{1}H NMR (500 MHz, $CDCl_3$)

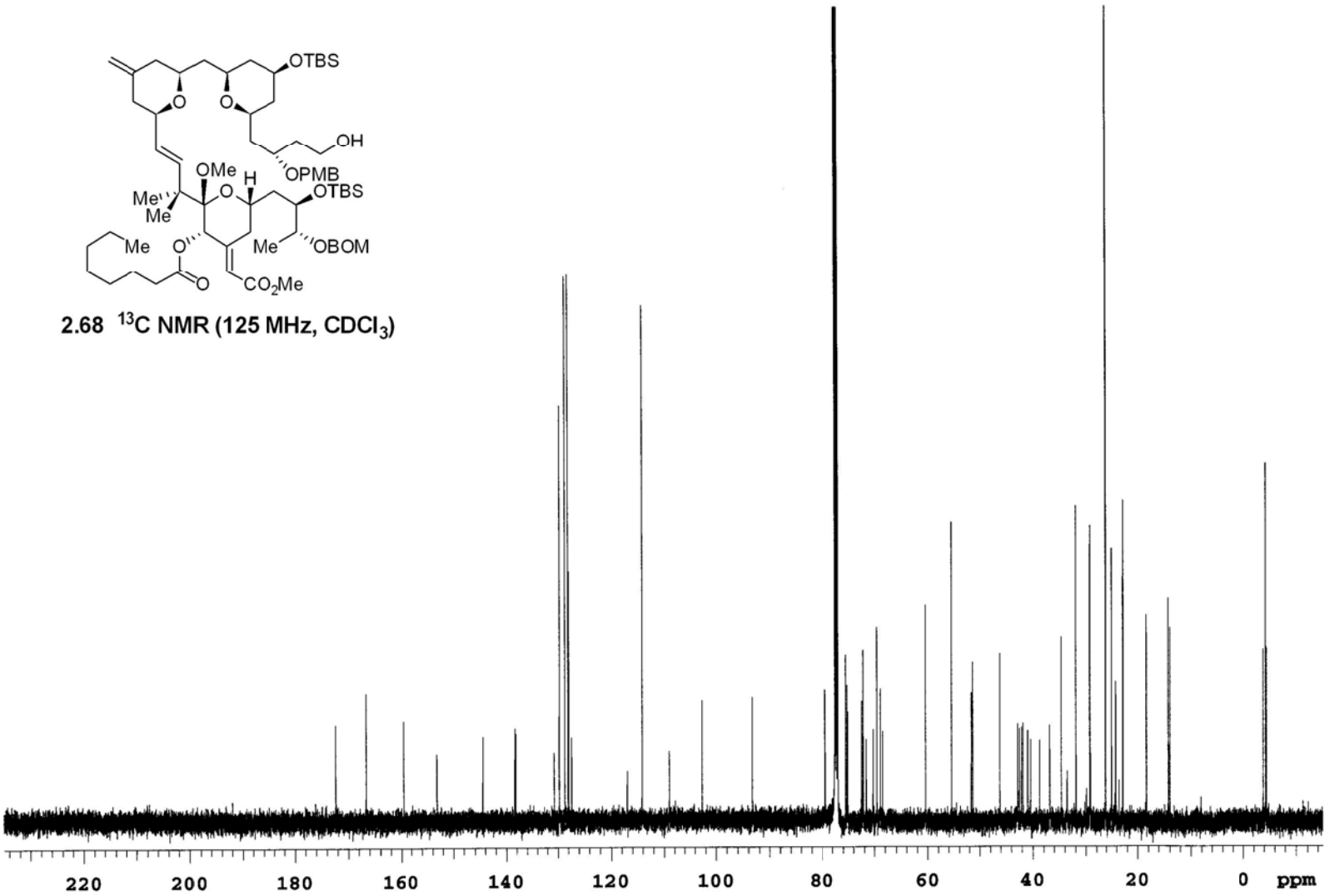


2.63 ^{13}C NMR (125 MHz, $CDCl_3$)

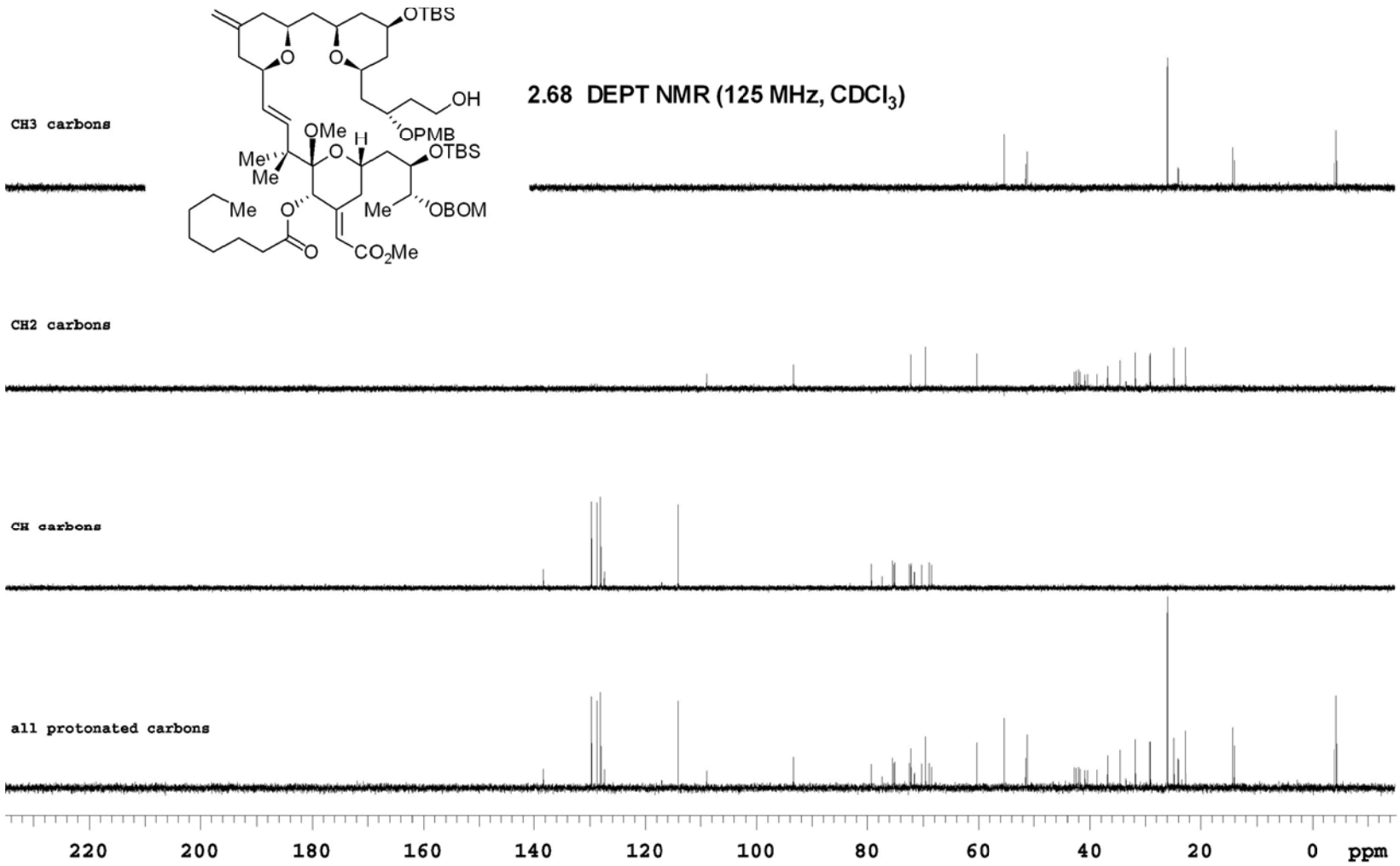

2.63 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OTBS
OTBDPS
OPMB
OTBS
OBOM
OMe
H
Me
Me
Me
Me
O
O
O
O
O
O
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

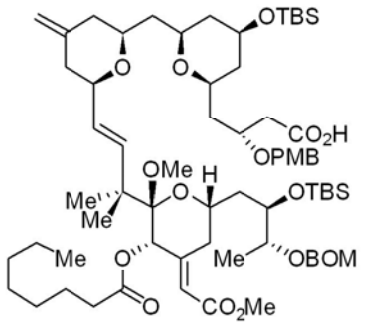


2.68 ^{1}H NMR (500 MHz, $CDCl_3$)

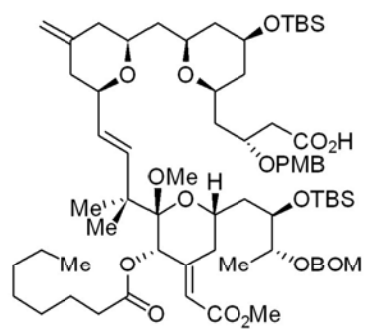


2.68 ^{13}C NMR (125 MHz, $CDCl_3$)

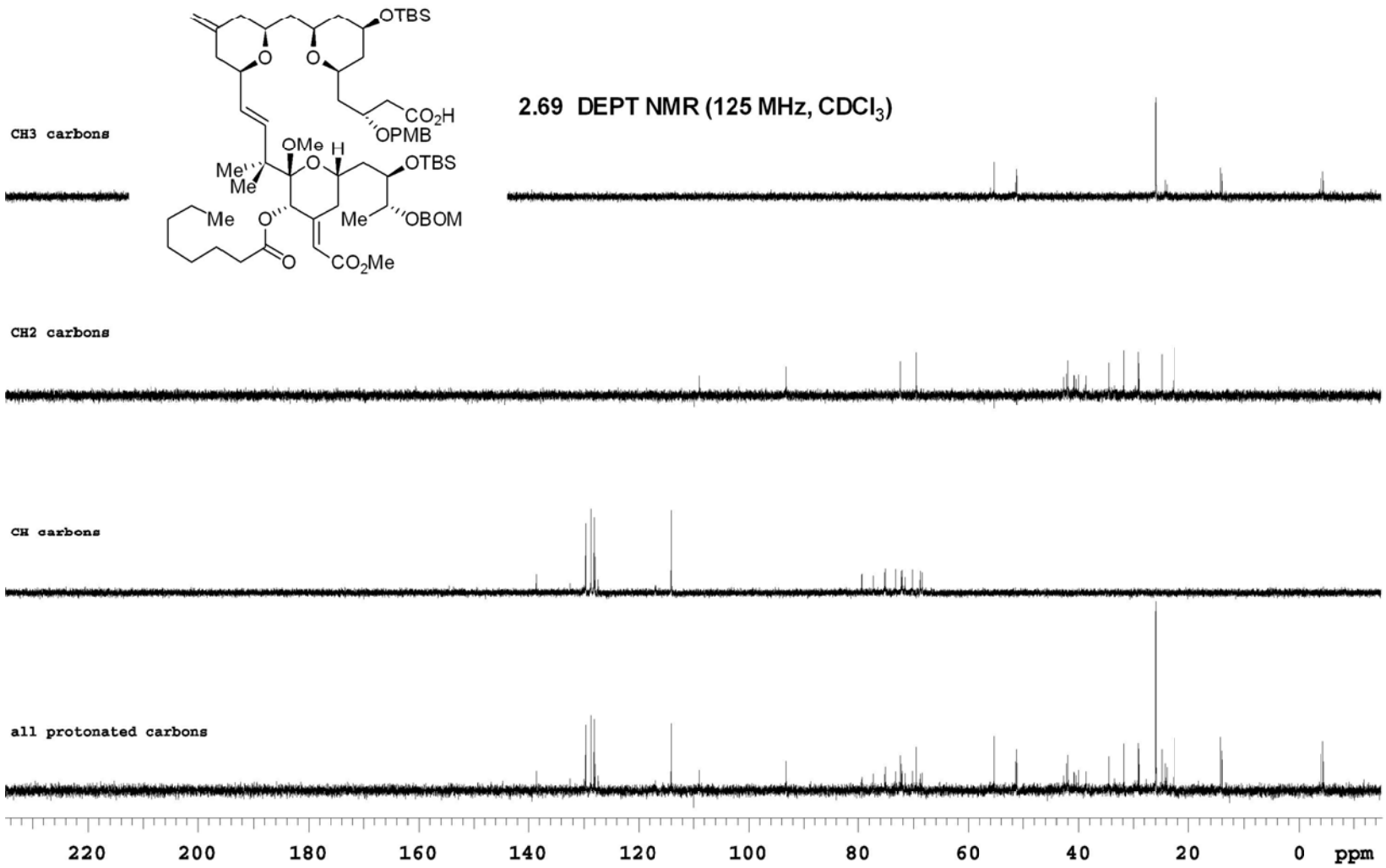

2.68 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OTBS
OH
OPMB
OTBS
OBOM
OMe
H
Me
Me
Me
Me
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

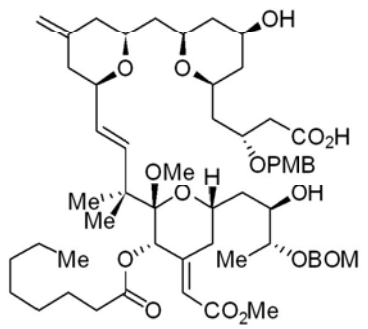


2.69 ^{1}H NMR (500 MHz, $CDCl_3$)

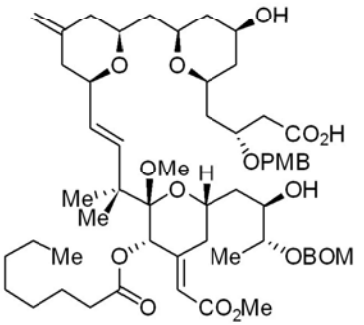


2.69 ^{13}C NMR (125 MHz, $CDCl_3$)

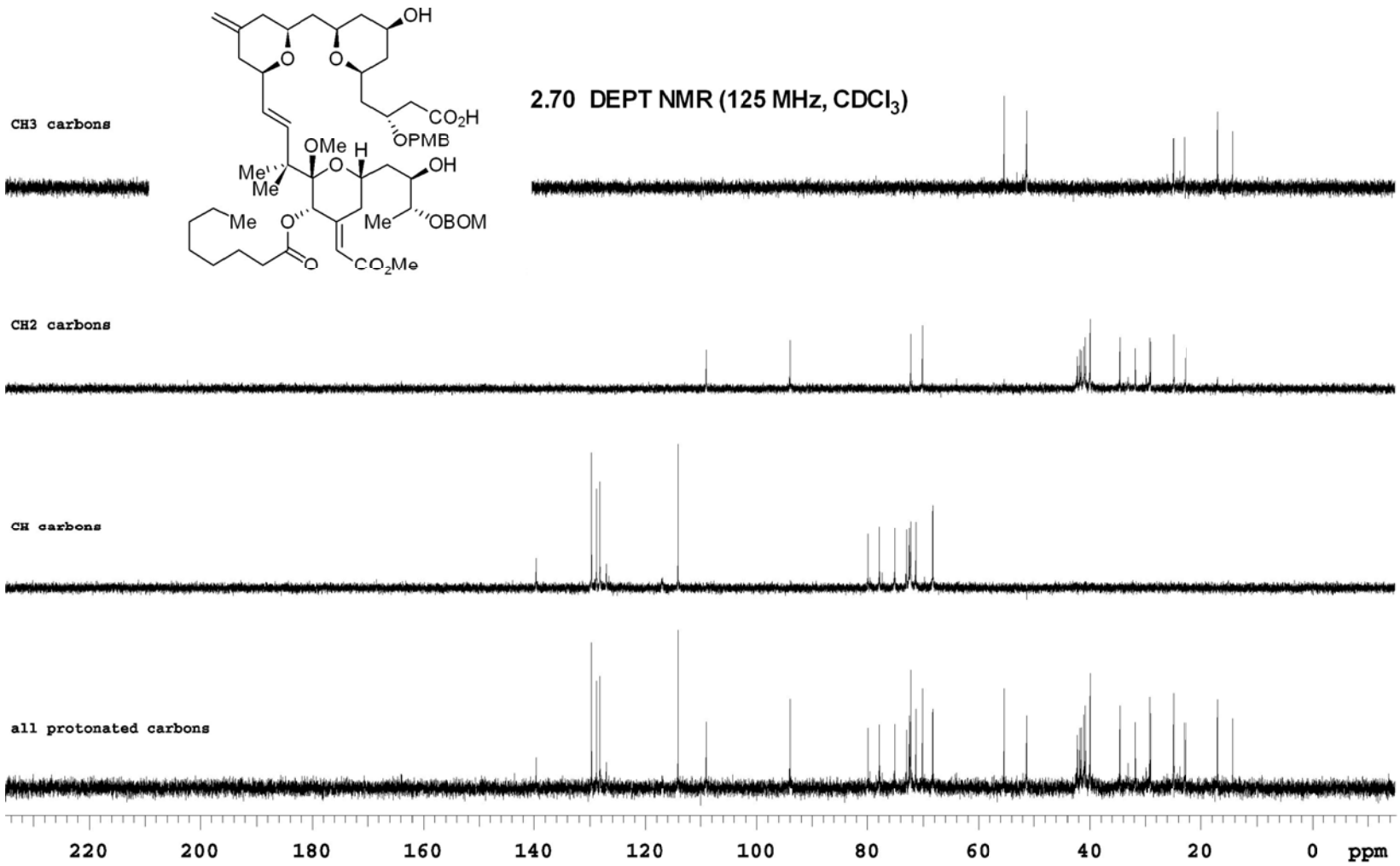

2.69 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OTBS
CO2H
OPMB
OMe
H
Me
Me
OTBS
Me
O
Me
OBOM
O
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

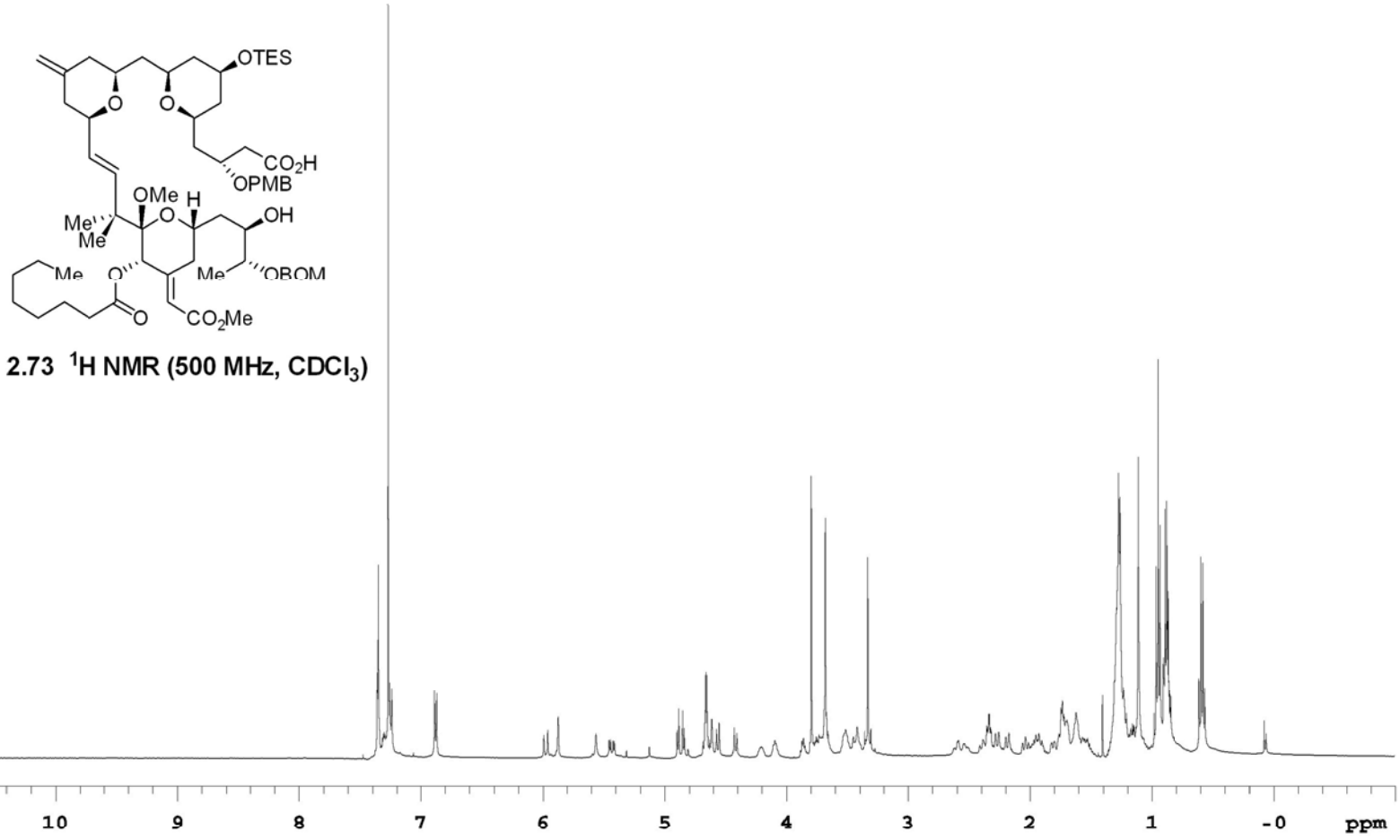


2.70 ^{1}H NMR (500 MHz, $CDCl_3$)

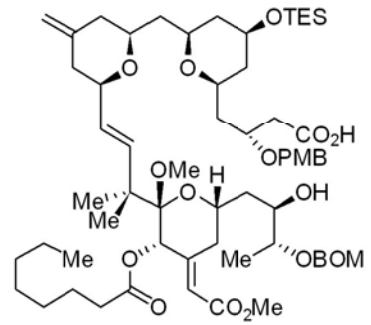


2.70 ^{13}C NMR (125 MHz, $CDCl_3$)

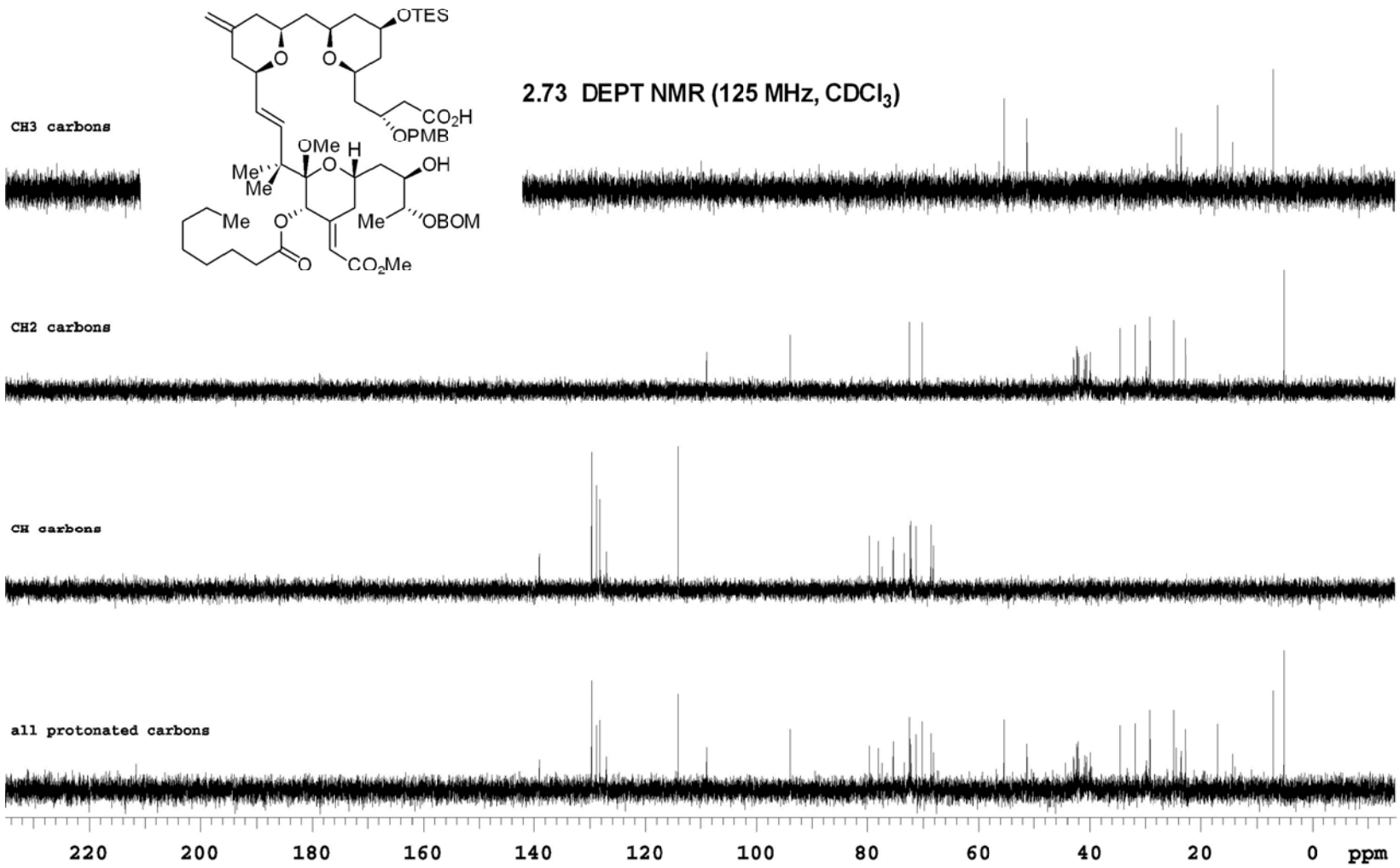

2.70 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OH
O
O
CO2H
OPMB
OMe
H
Me
Me
O
OH
Me
O
Me
OBOM
O
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

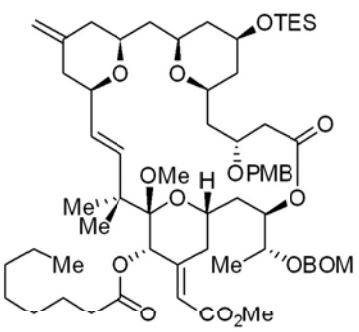


2.73 ^{1}H NMR (500 MHz, $CDCl_3$)

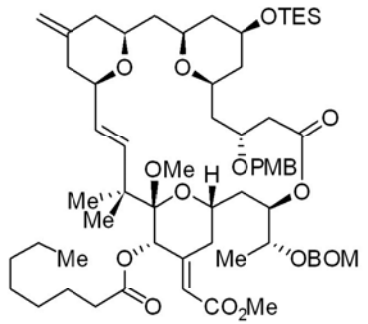


2.73 ^{13}C NMR (125 MHz, $CDCl_3$)

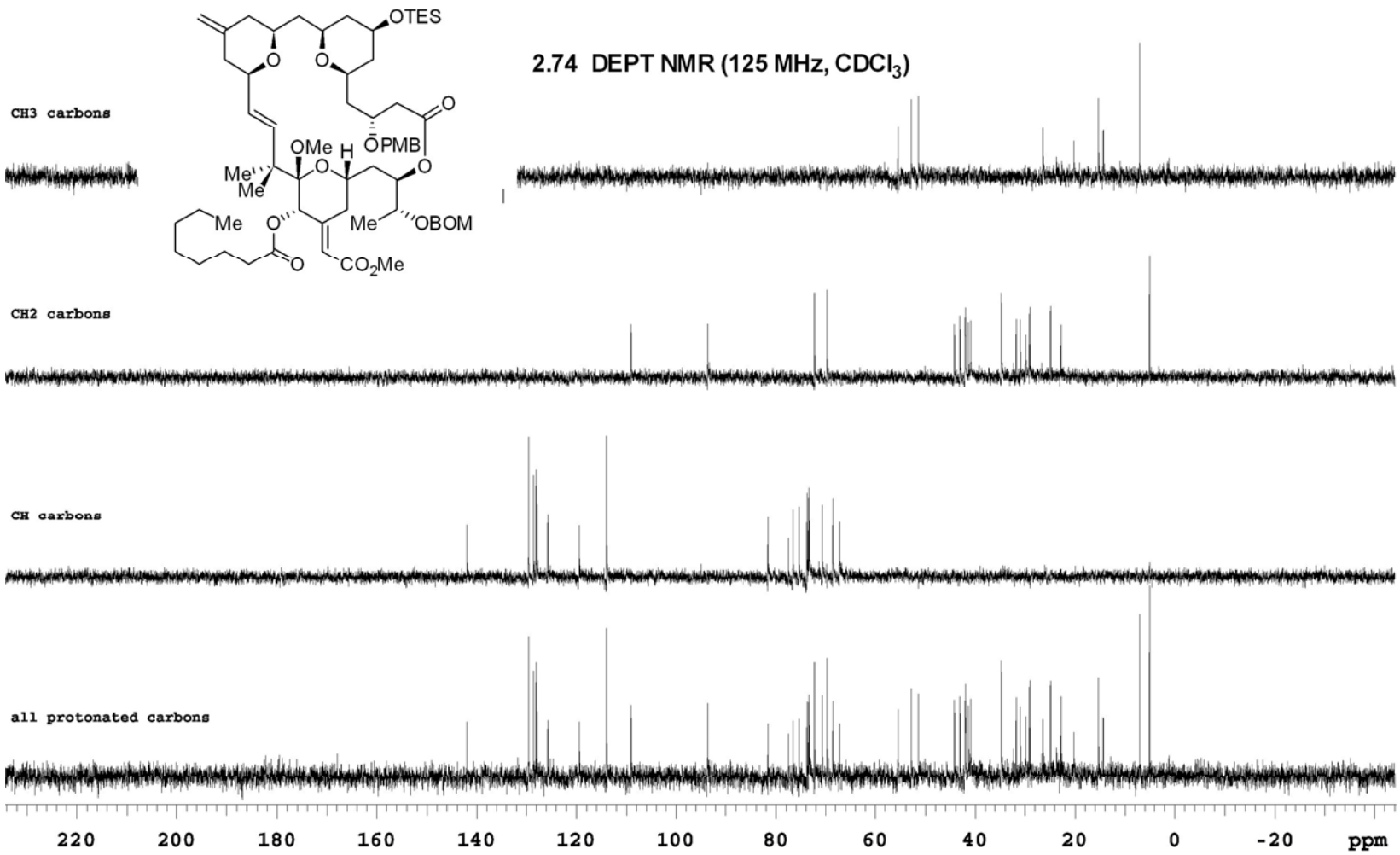

2.73 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OTES
CO2H
OPMB
OMe
H
OH
Me
Me
Me
OBOM
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

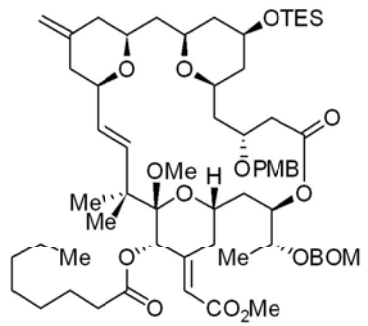


2.74 ^{1}H NMR (500 MHz, $CDCl_3$)

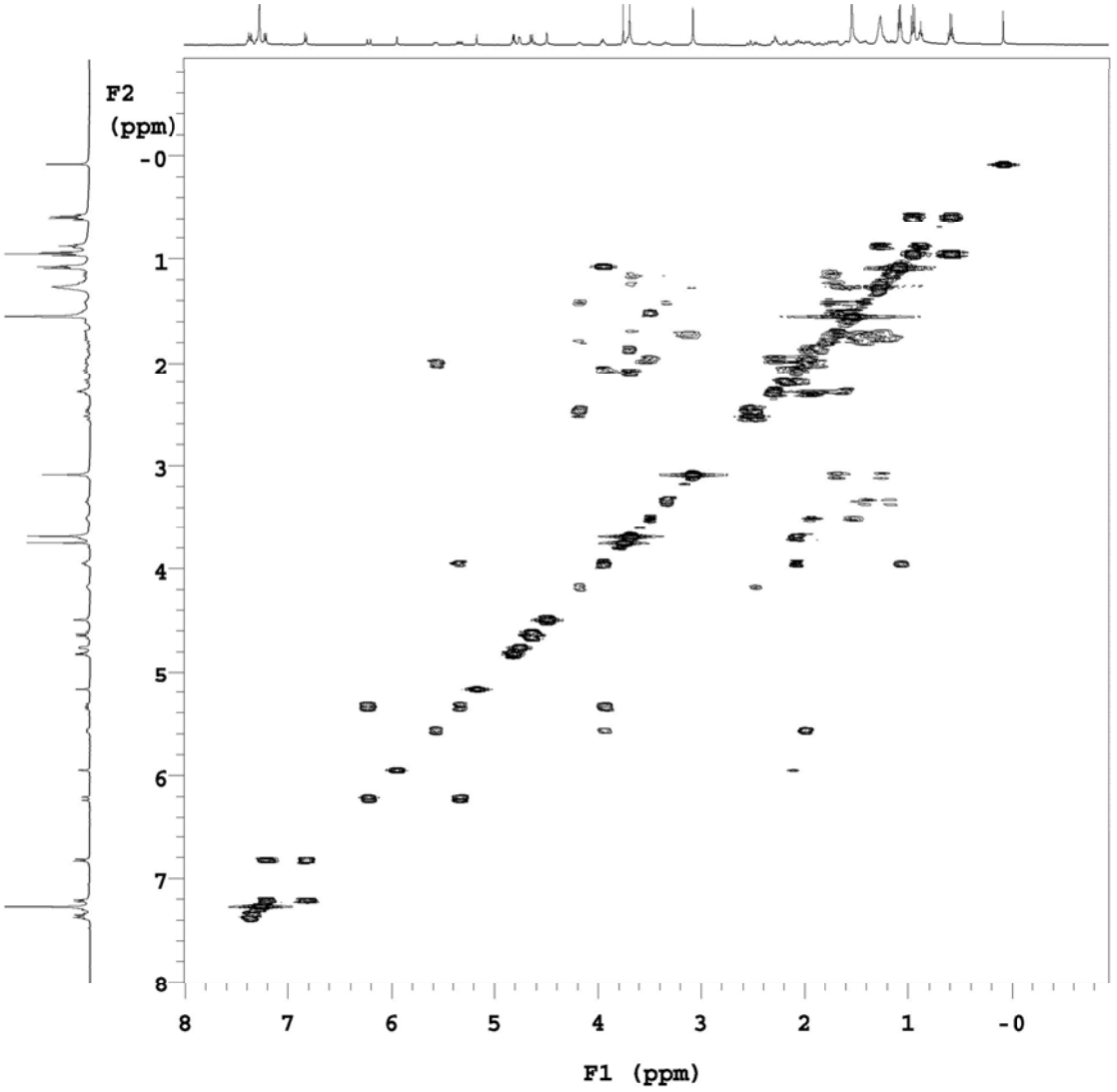


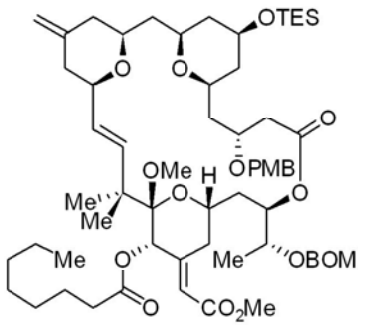
2.74 ^{13}C NMR (125 MHz, $CDCl_3$)

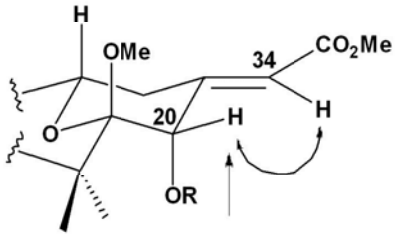

2.74 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OTES
OMe
H
OPMB
Me
Me
Me
O
Me
OBOM
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm



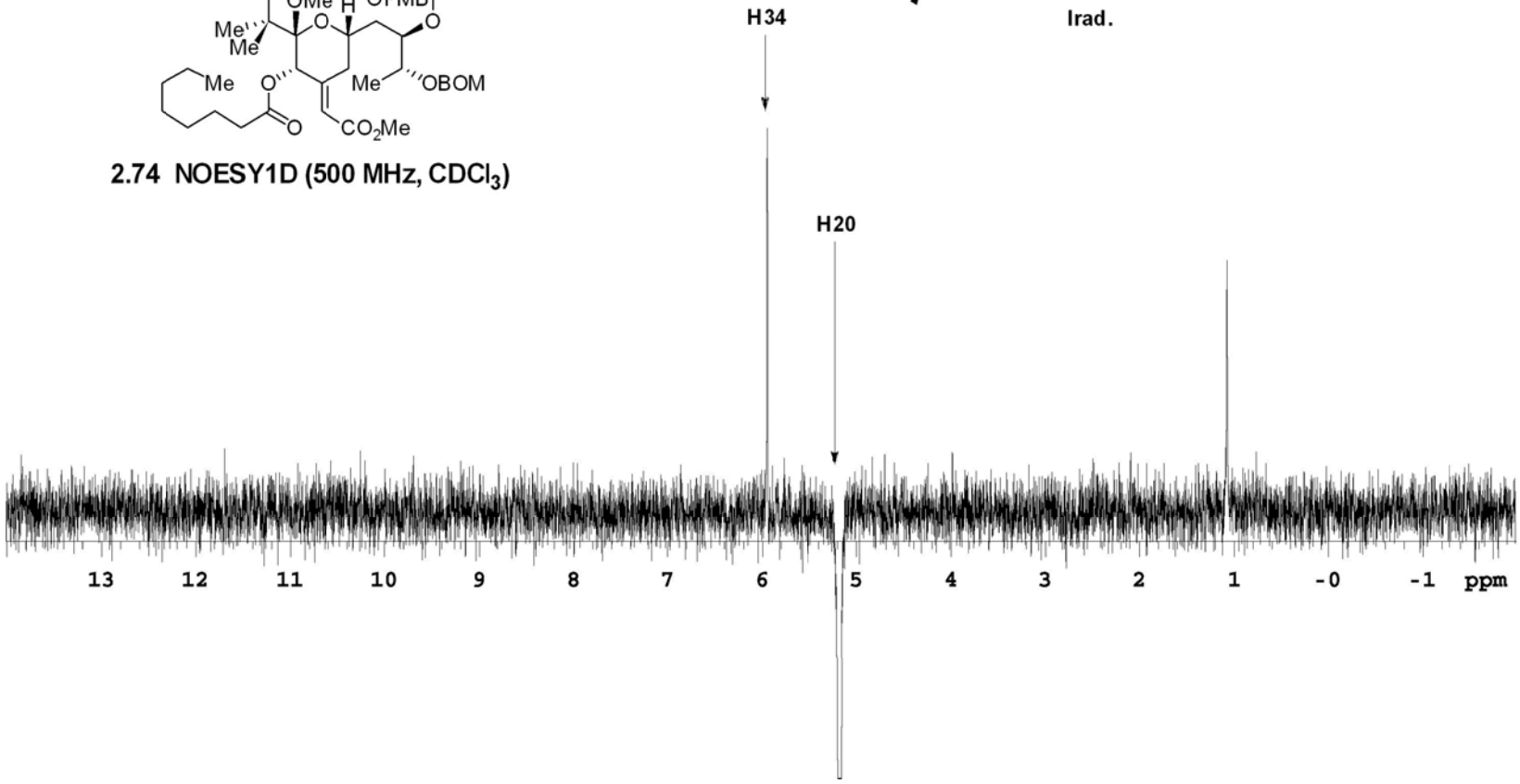
2.74 gCOSY (500 MHz, $CDCl_3$)

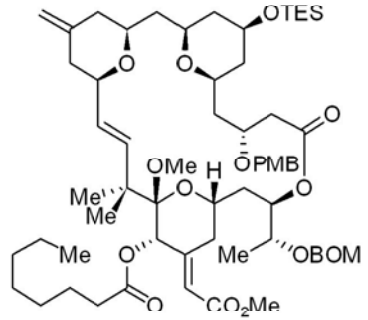


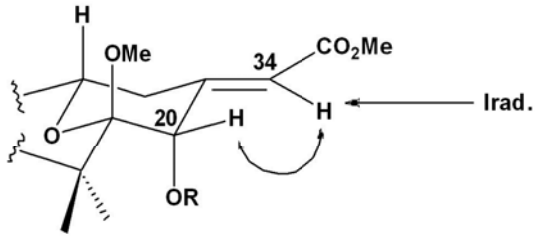




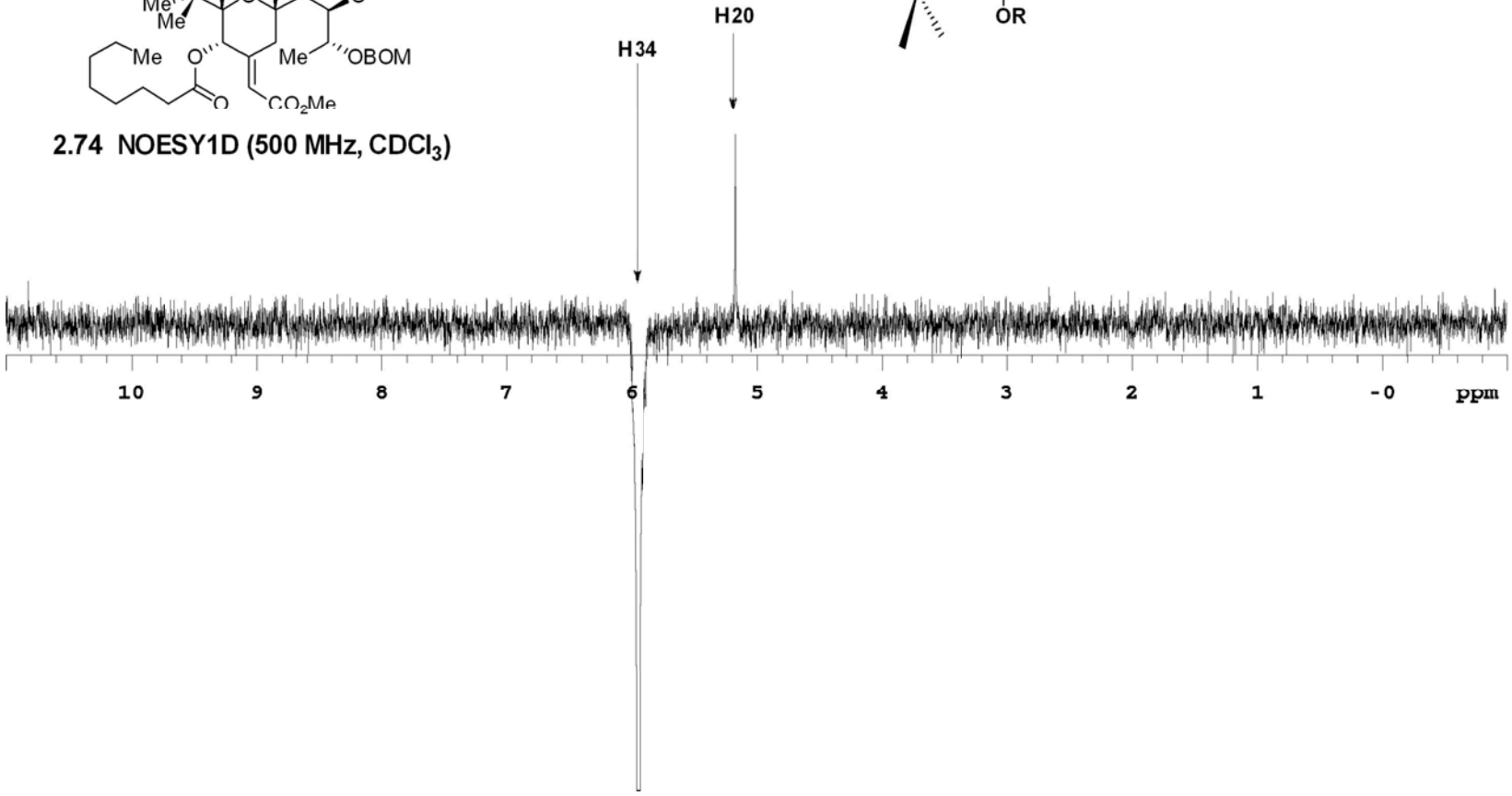
2.74 NOESY1D (500 MHz, $CDCl_3$)

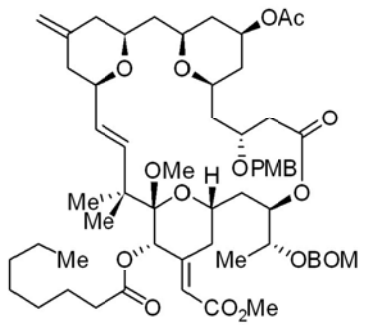




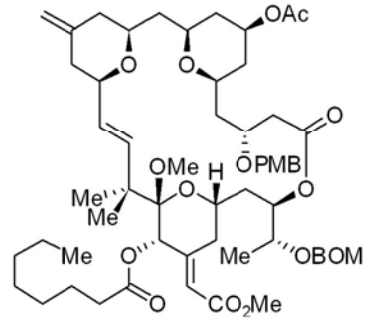


2.74 NOESY1D (500 MHz, $CDCl_3$)

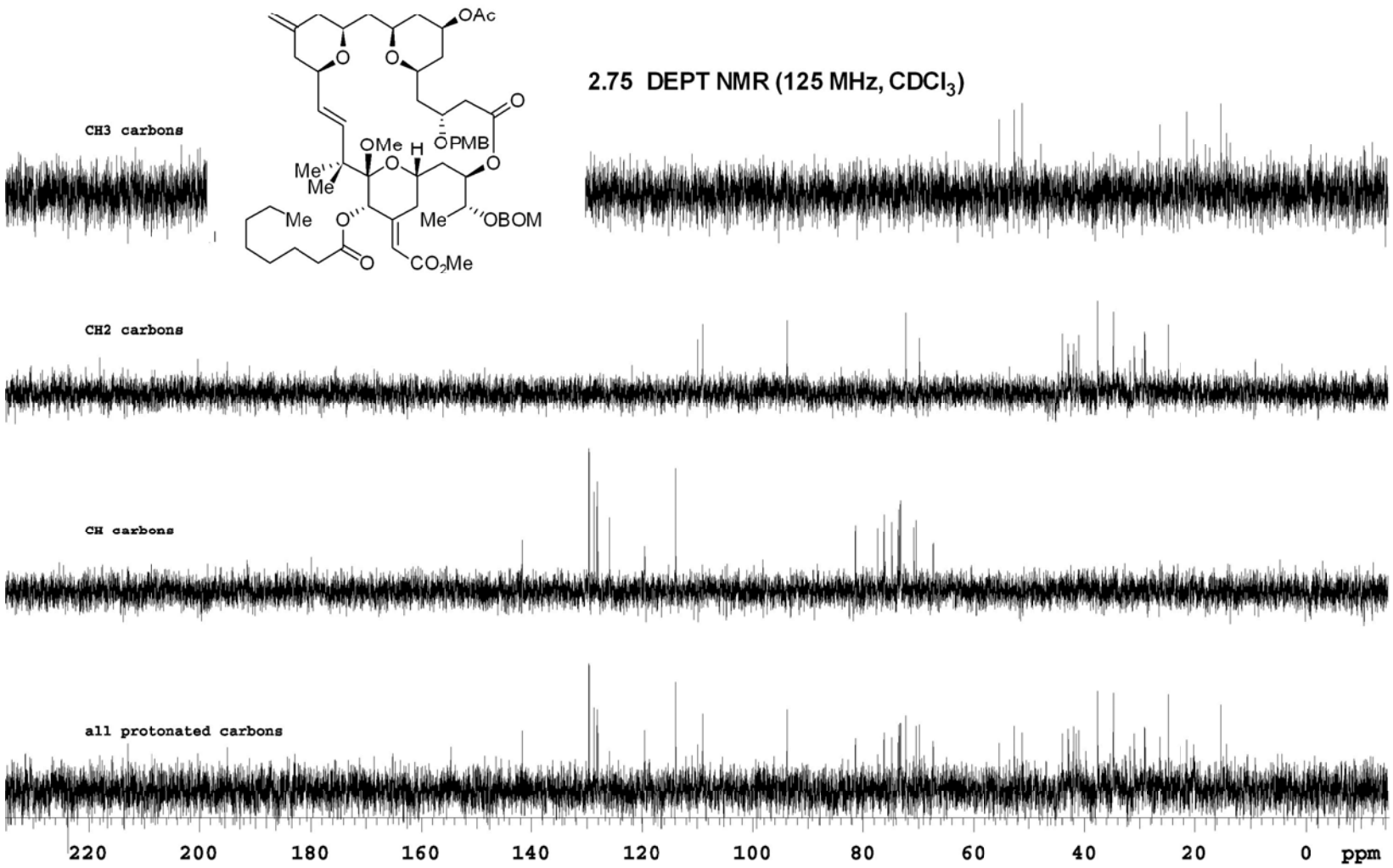


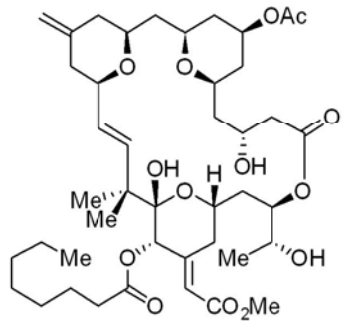


2.75 ^{1}H NMR (500 MHz, $CDCl_3$)

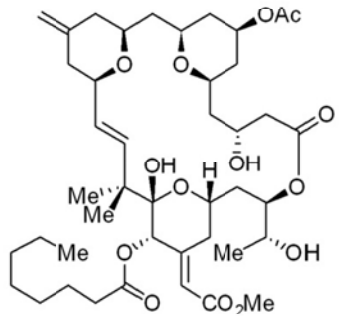


2.75 ^{13}C NMR (125 MHz, $CDCl_3$)

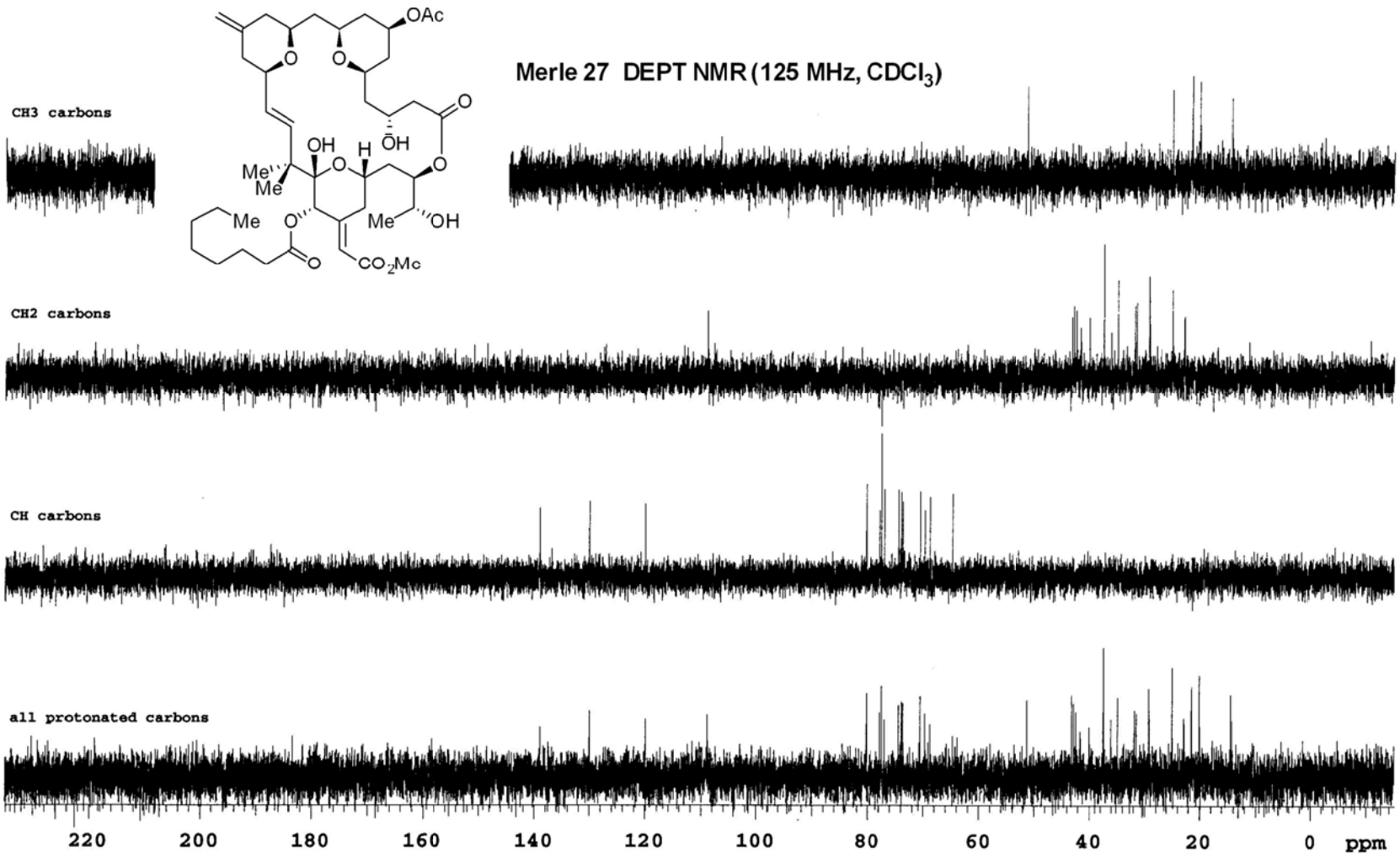

2.75 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OAc
OMe
H
OPMB
Me
Me
Me
OBOM
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

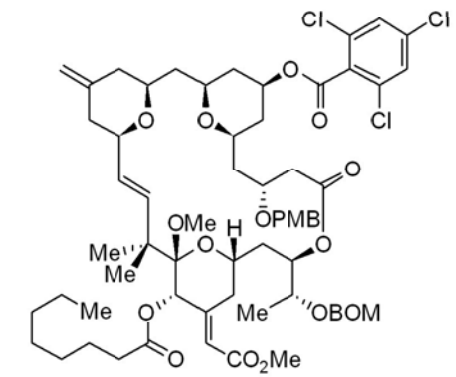


Merle 27 ^{1}H NMR (500 MHz, $CDCl_3$)

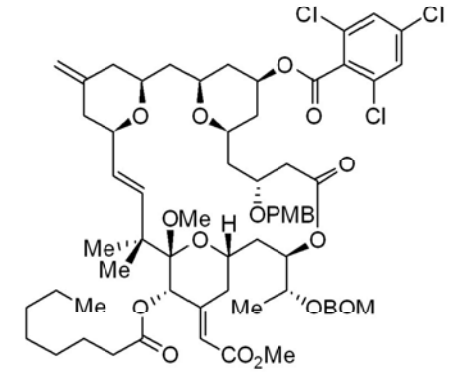


Merle 27 ^{13}C NMR (125 MHz, $CDCl_3$)

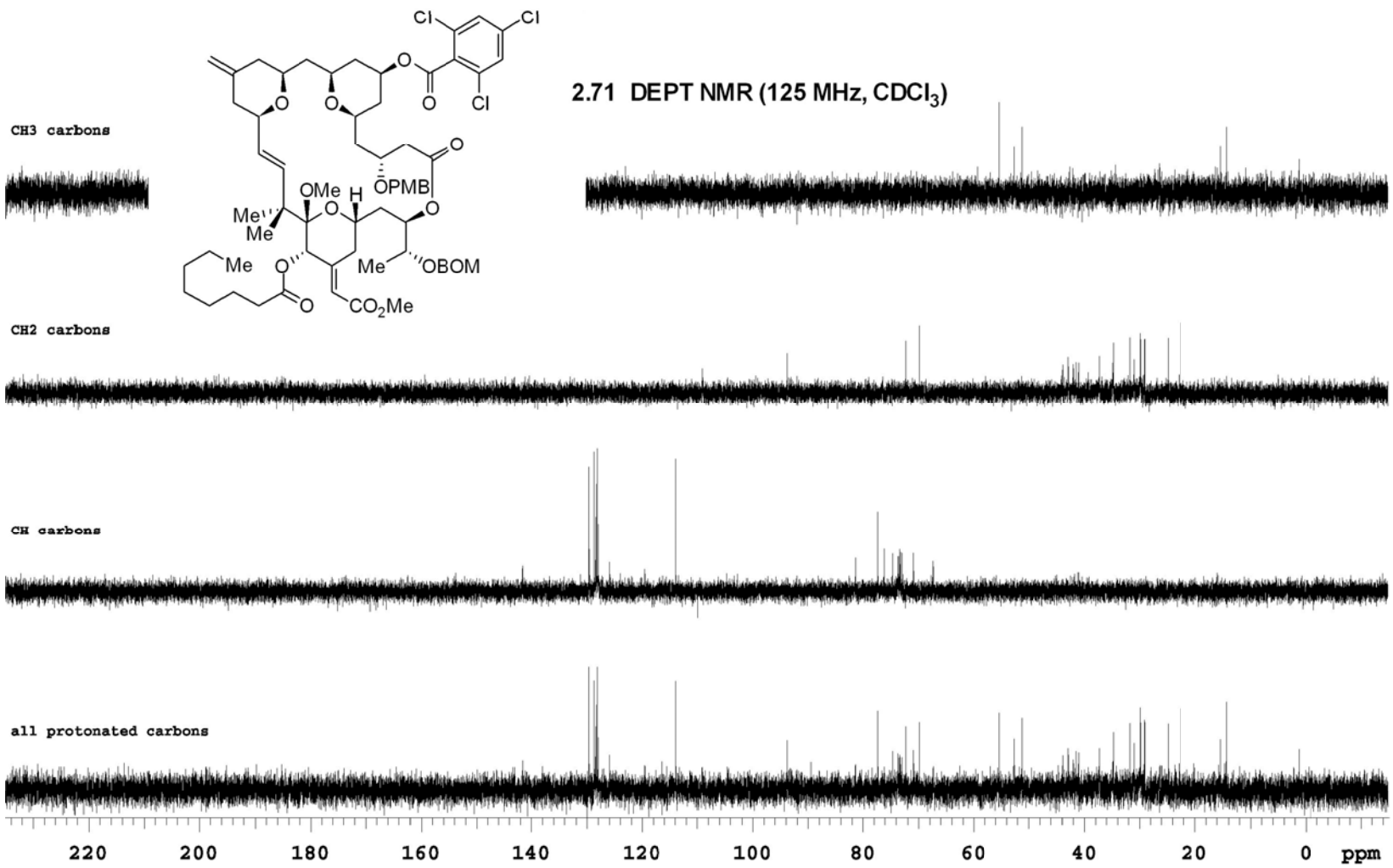

Merle 27 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OAc
OH
H
OH
Me
Me
Me
OH
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
ppm

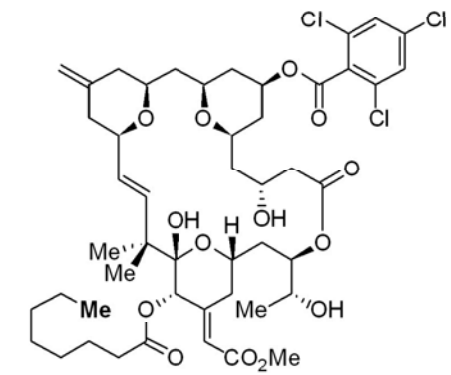


2.71 ^{1}H NMR (500 MHz, $CDCl_3$)

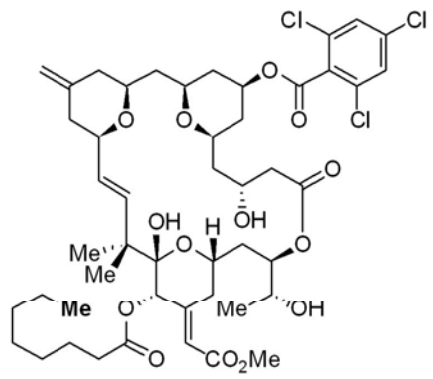


2.71 ^{13}C NMR (125 MHz, $CDCl_3$)

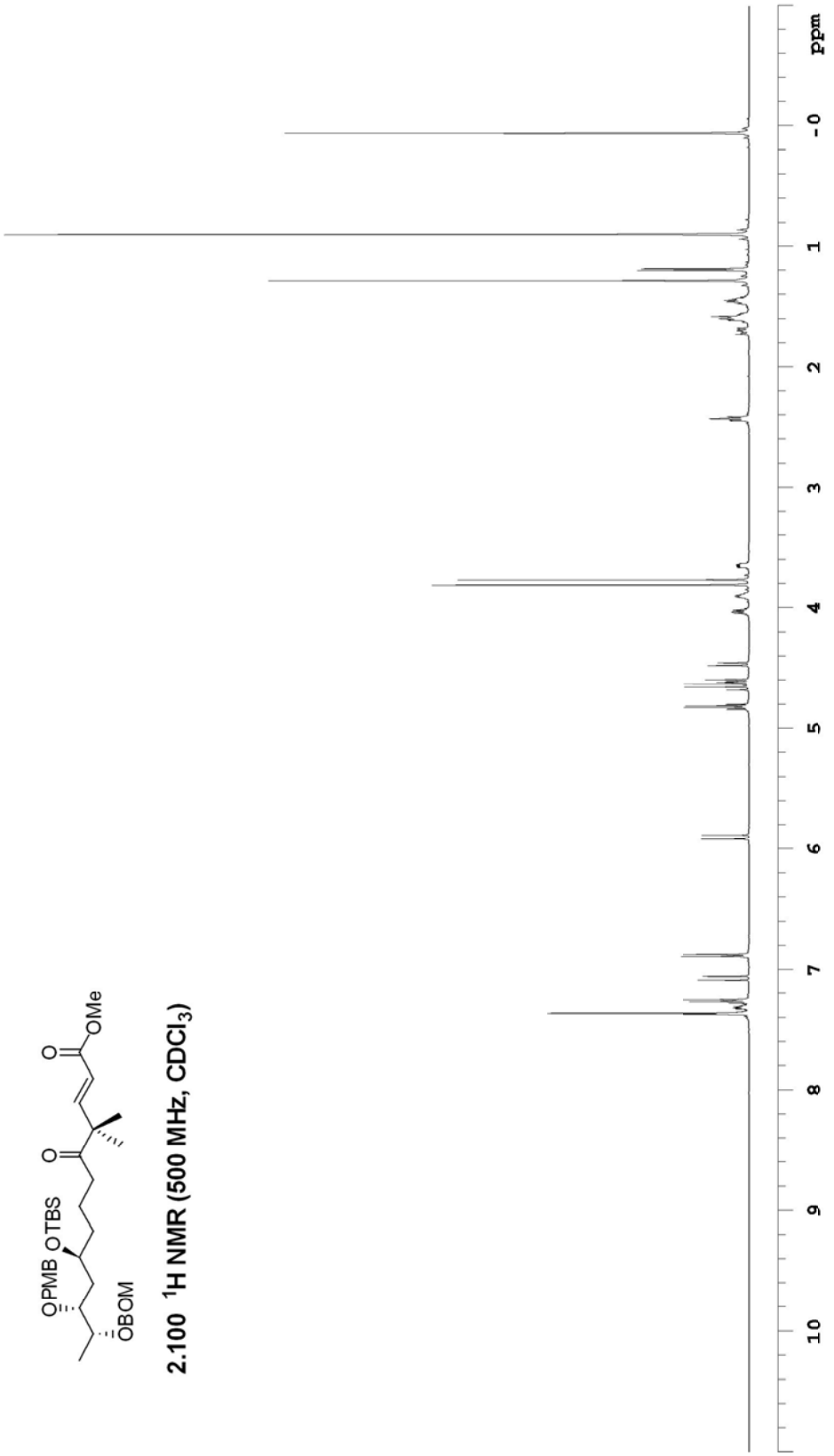

2.71 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
ppm



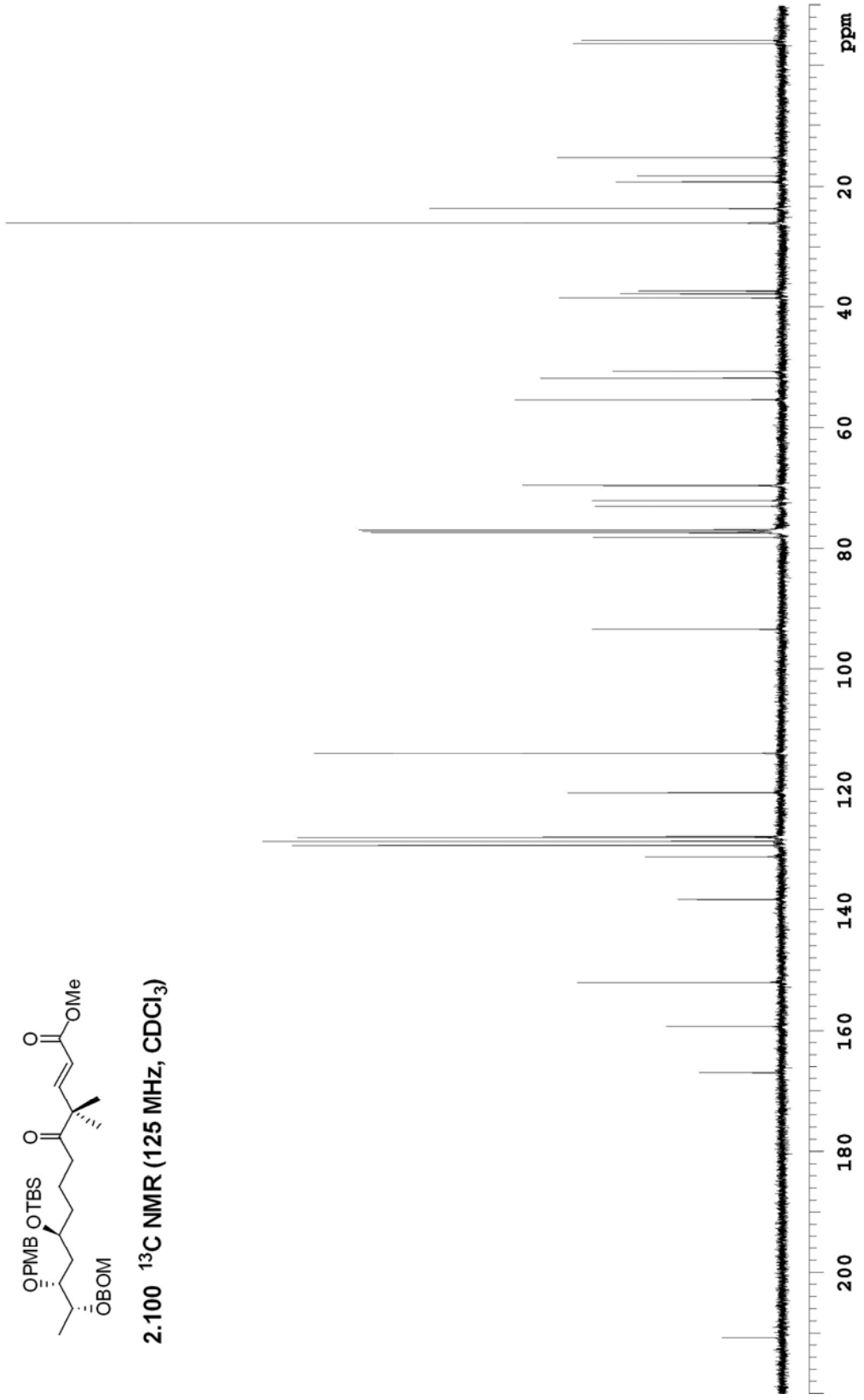
2.72 ^{1}H NMR (500 MHz, $CDCl_3$)



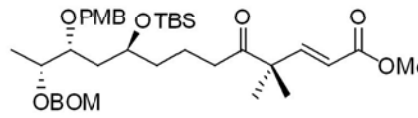
2.72 ^{13}C NMR (125 MHz, $CDCl_3$)



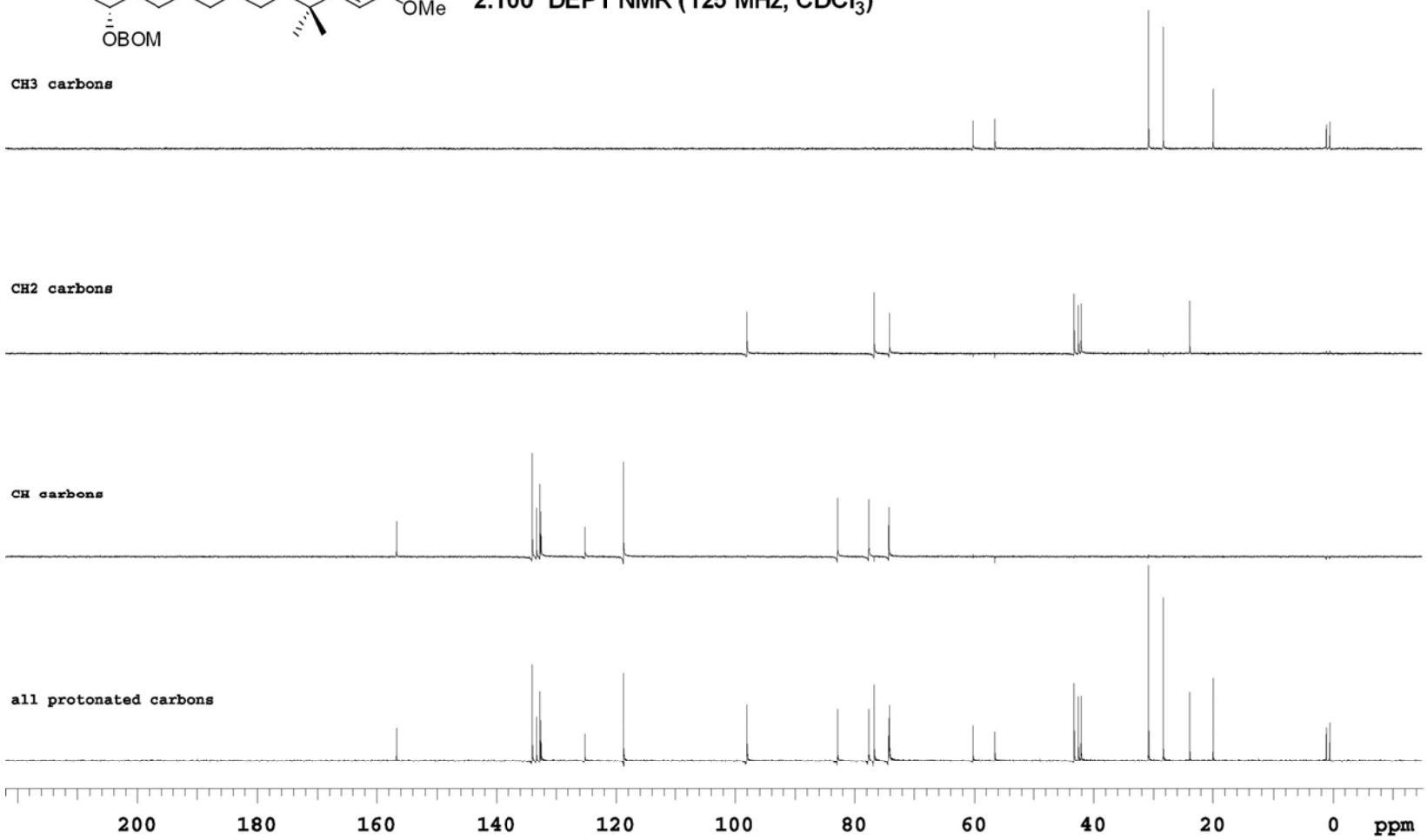
2.100 ^{1}H NMR (500 MHz, $CDCl_3$)

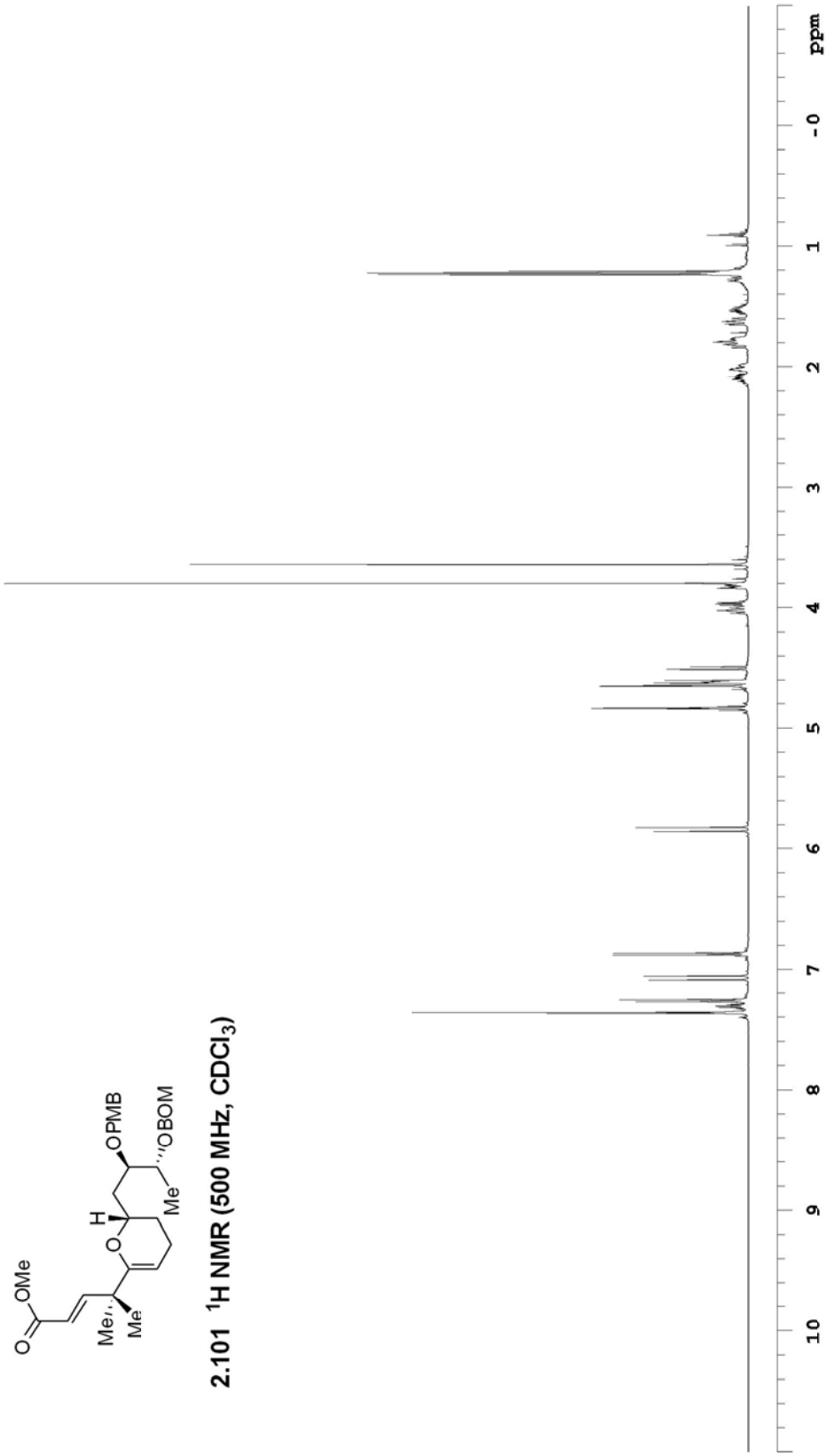


2.100 ^{13}C NMR (125 MHz, $CDCl_3$)

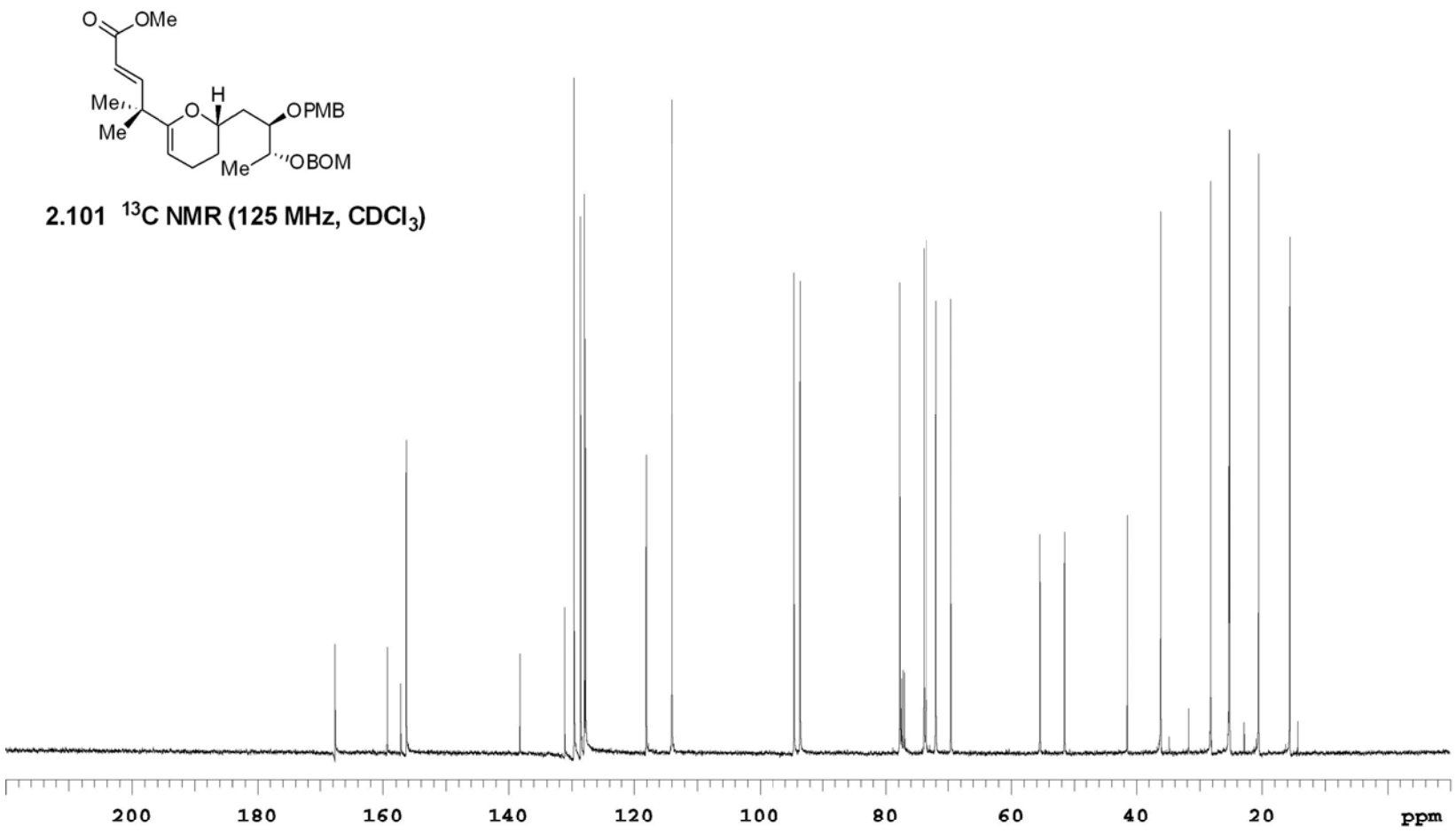


2.100 DEPT NMR (125 MHz, $CDCl_3$)

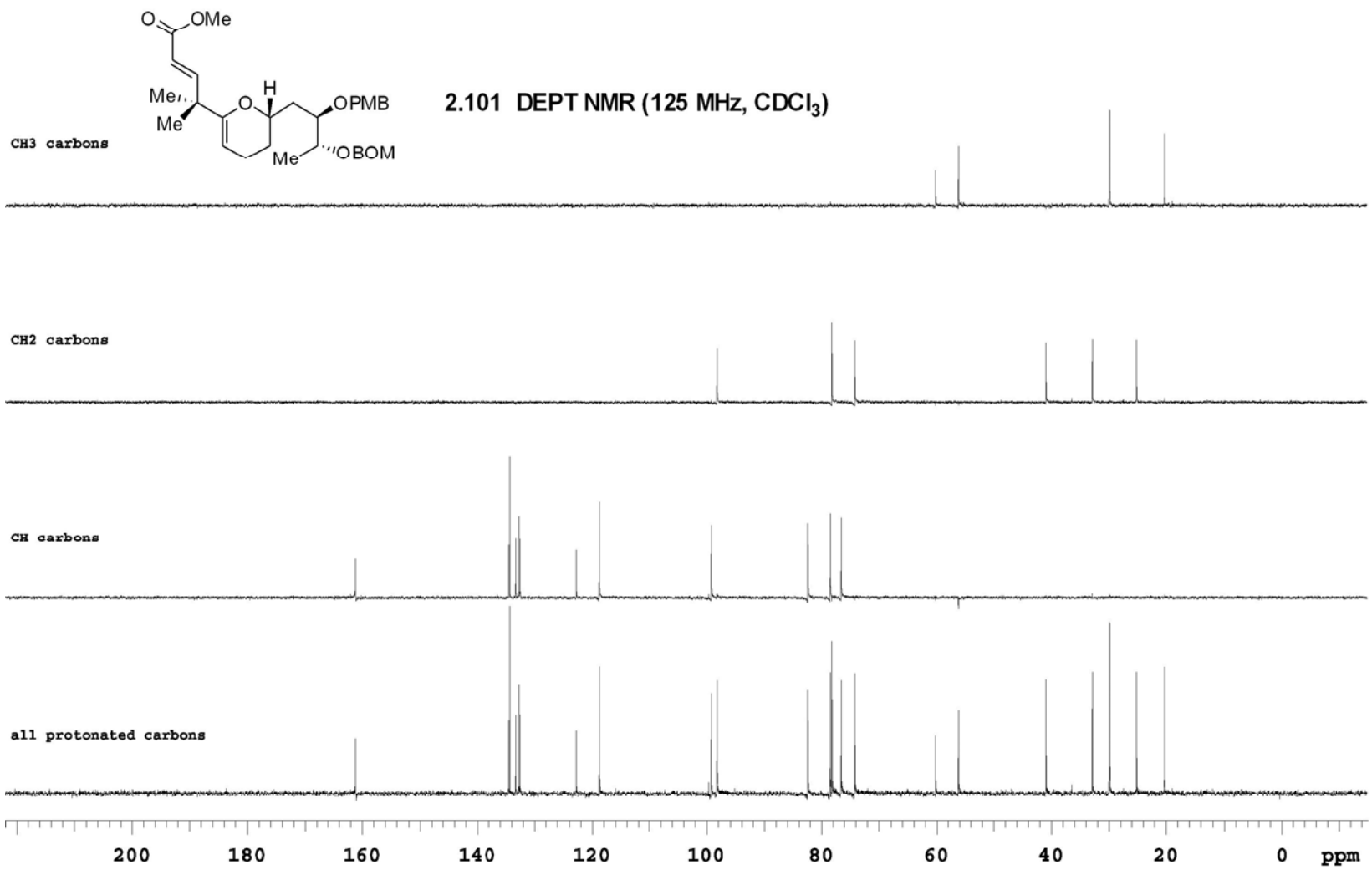


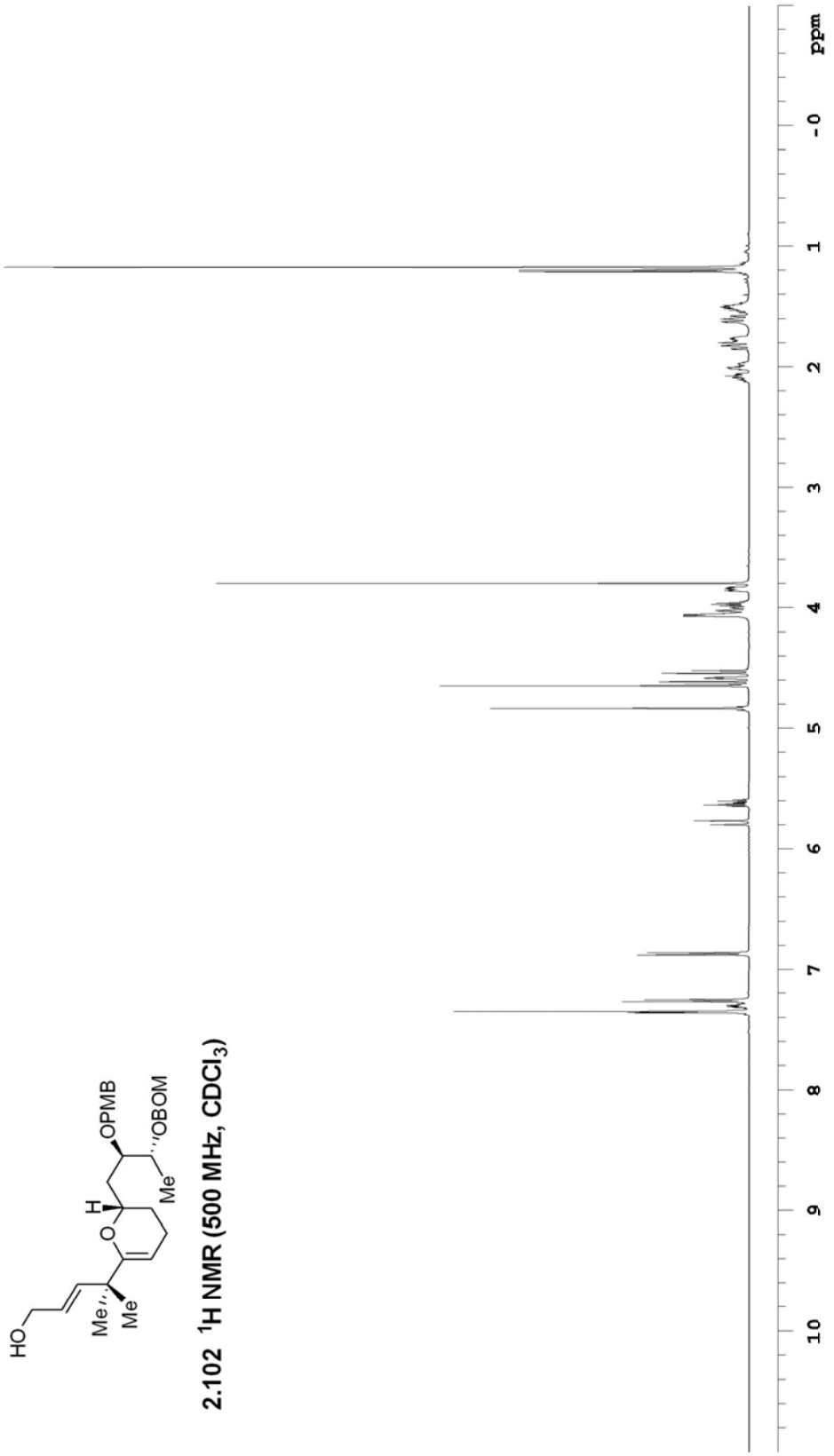


2.101 ^{1}H NMR (500 MHz, $CDCl_3$)

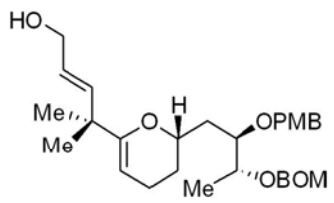


2.101 ^{13}C NMR (125 MHz, $CDCl_3$)

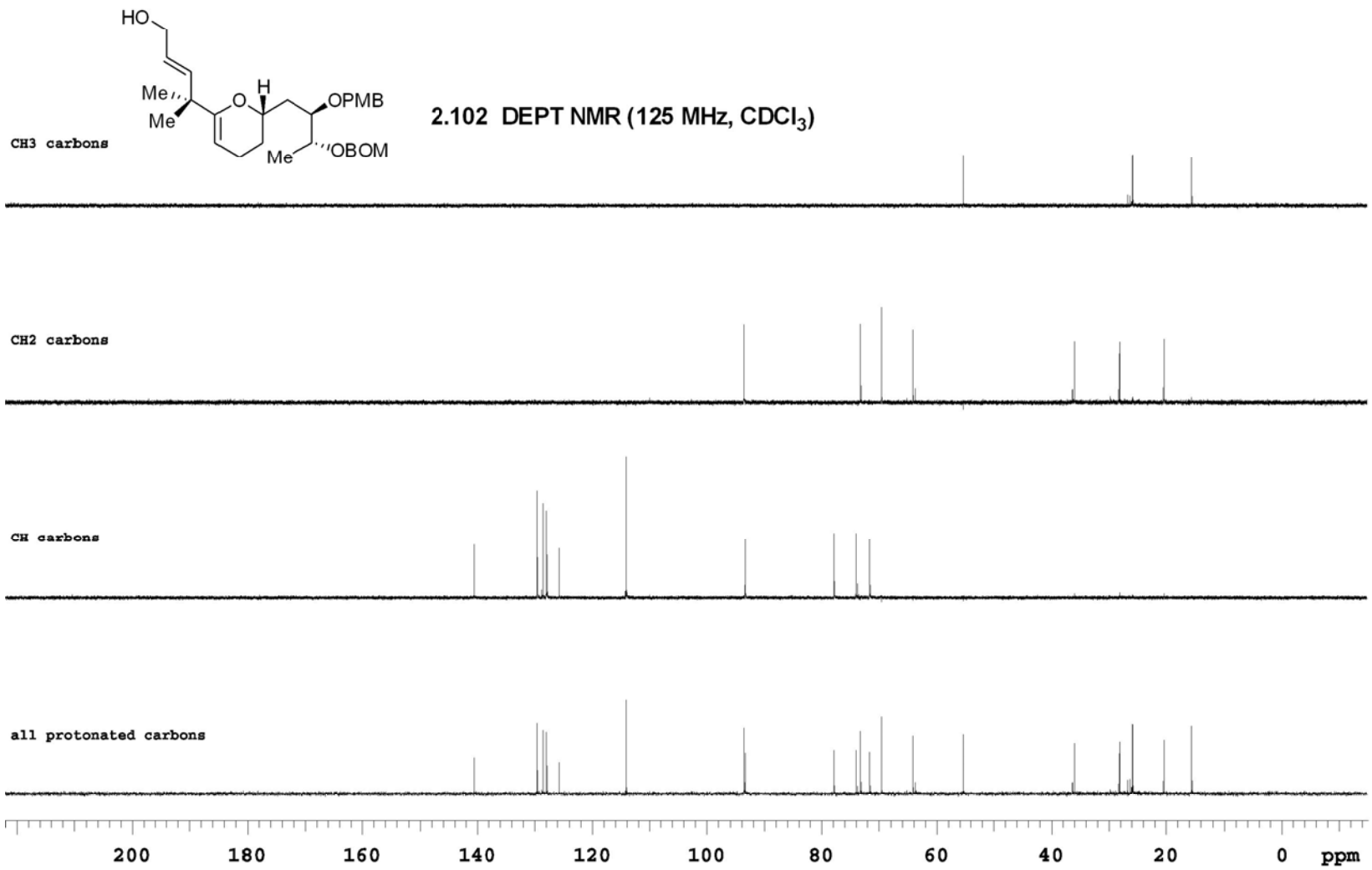

O
OMe
Me
Me
O
H
OPMB
Me
OBOM
2.101 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

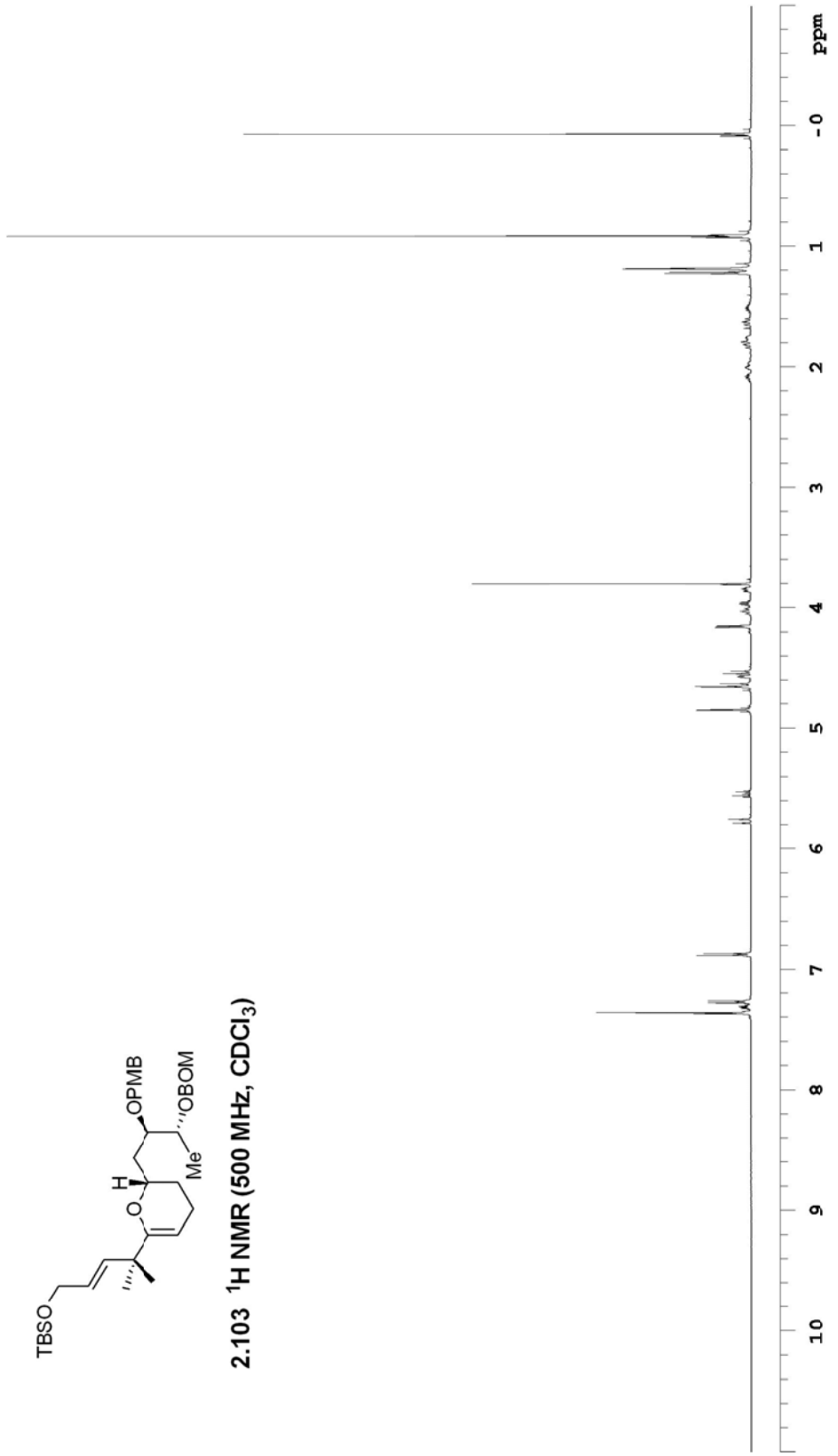


2.102 ^{1}H NMR (500 MHz, $CDCl_3$)

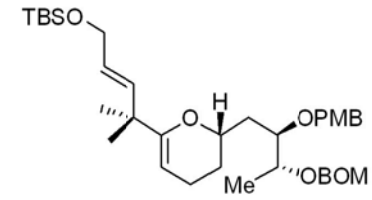


2.102 ^{13}C NMR (125 MHz, $CDCl_3$)

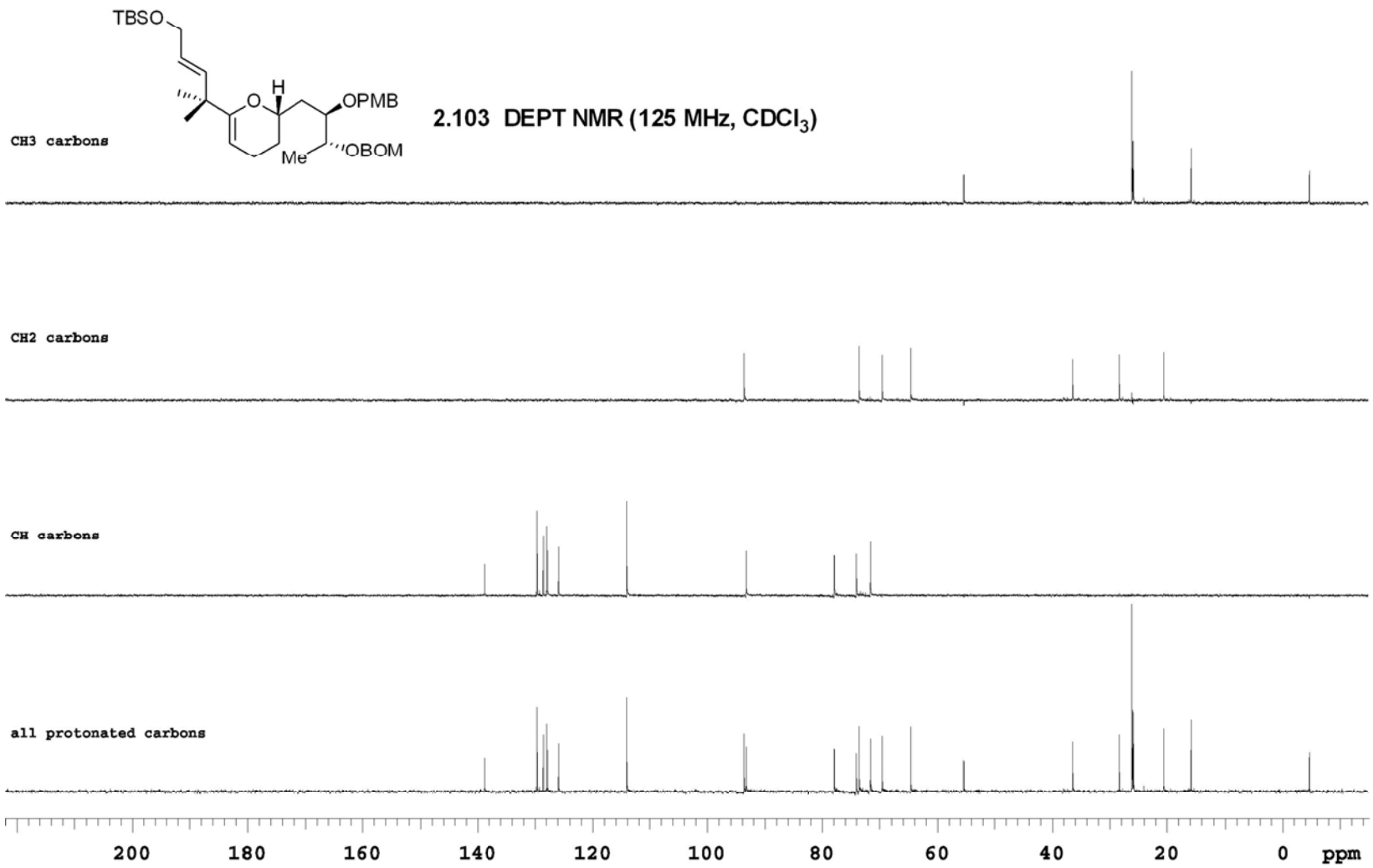

HO
Me
Me
O
H
OPMB
Me
OBOM
2.102 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

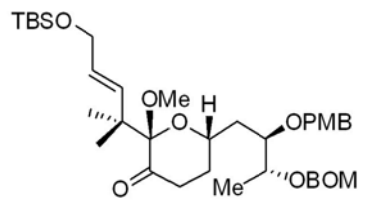


2.103 ^{1}H NMR (500 MHz, $CDCl_3$)

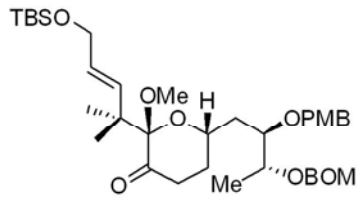


2.103 ^{13}C NMR (125 MHz, $CDCl_3$)

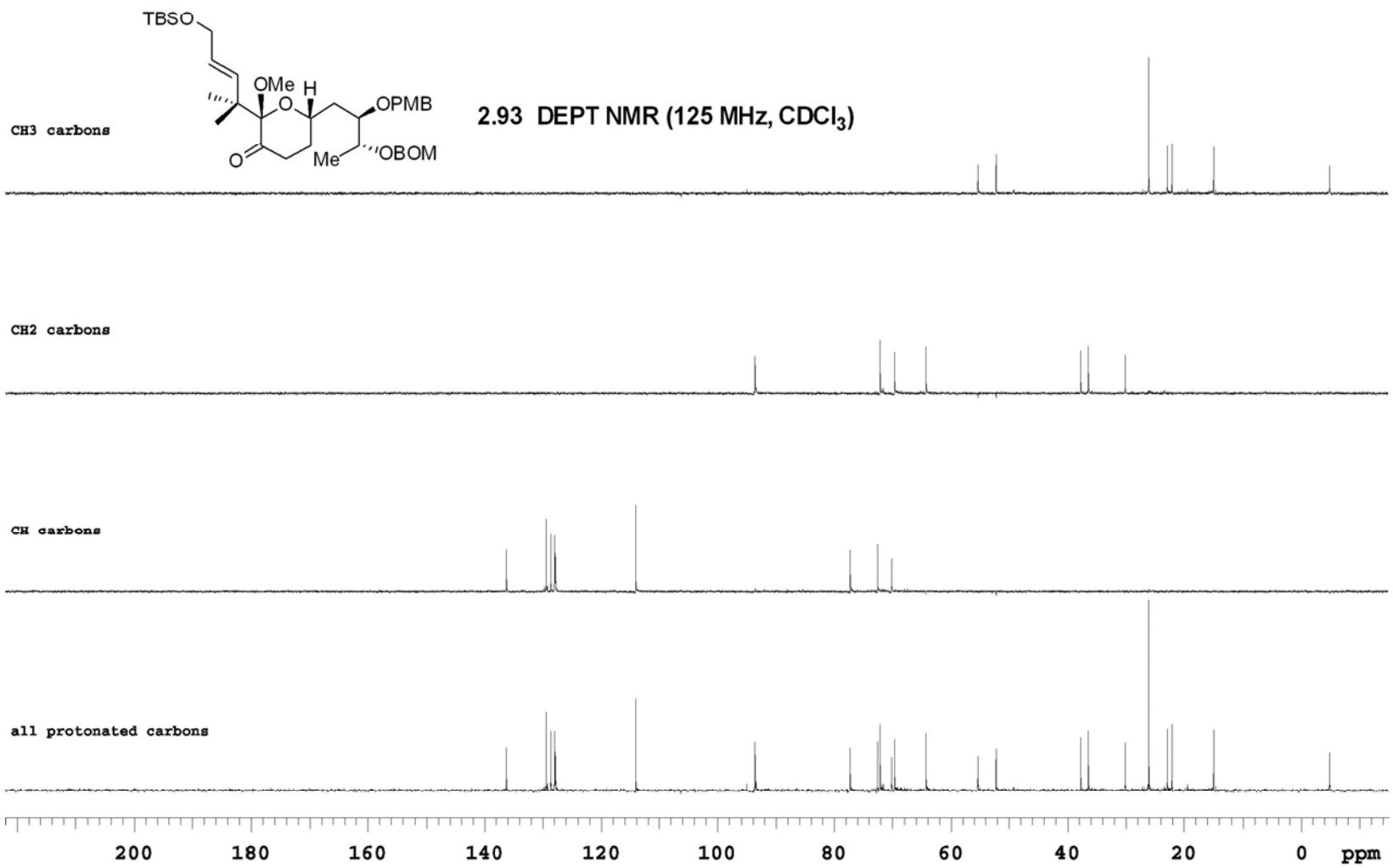

TBSO
H
O
OPMB
Me
OBOM
2.103 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

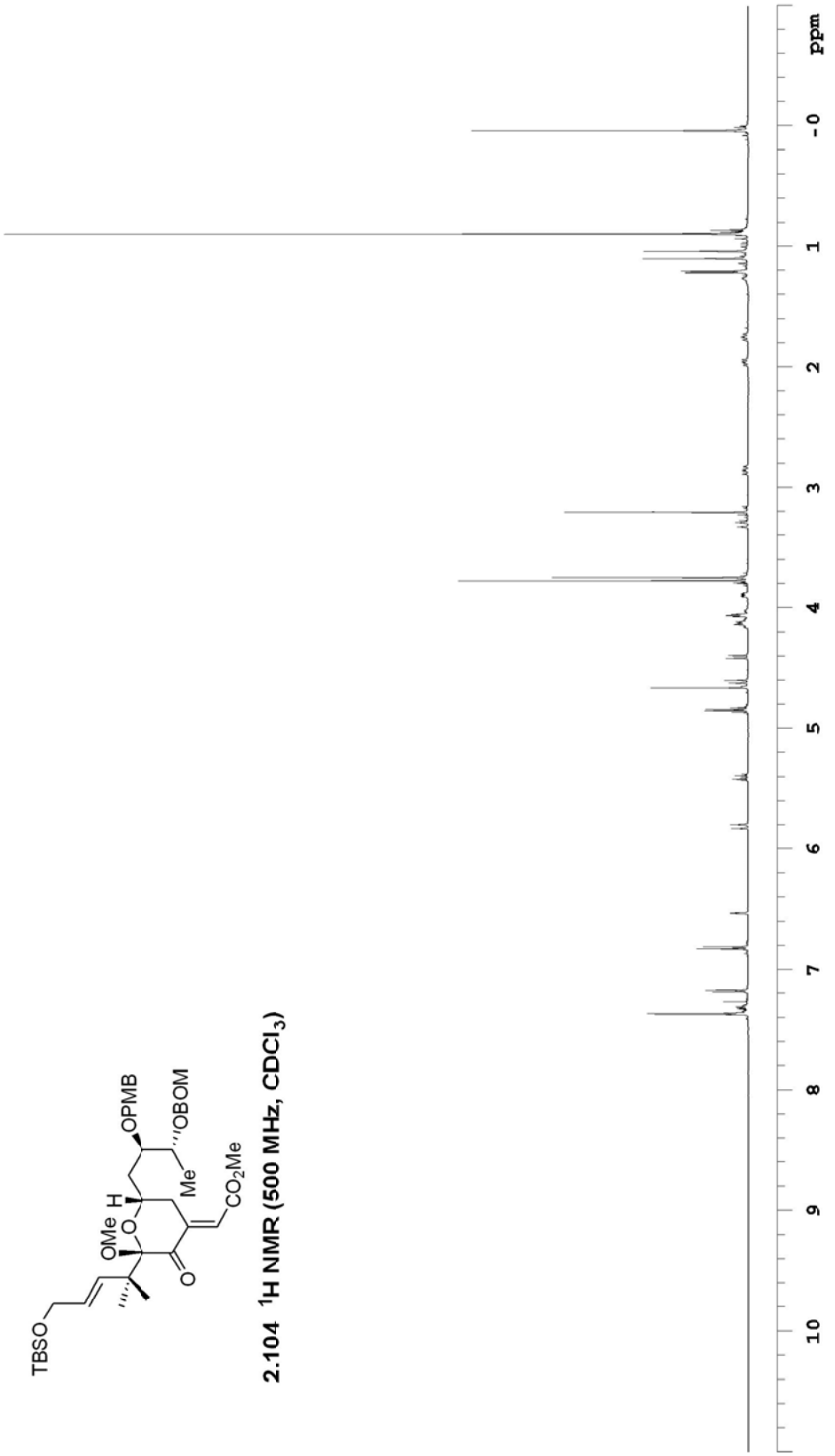


2.93 ^{1}H NMR (500 MHz, $CDCl_3$)

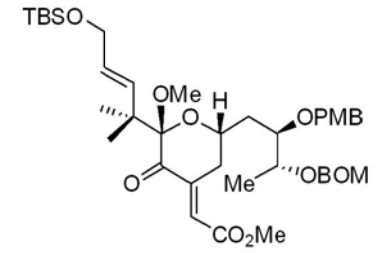


2.93 ^{13}C NMR (125 MHz, $CDCl_3$)

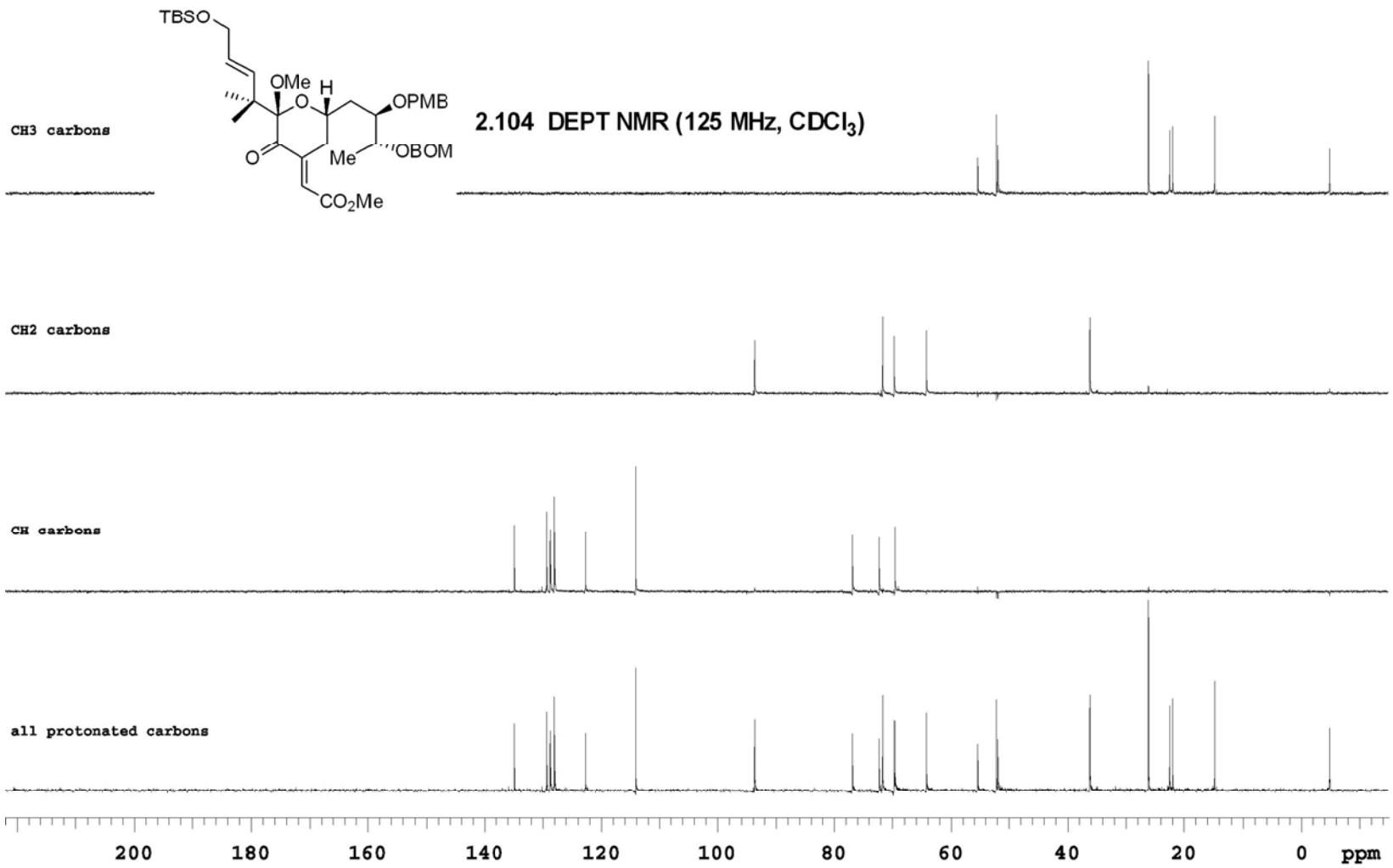

TBSO
OMe
H
O
OPMB
O
Me
OBOM
2.93 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

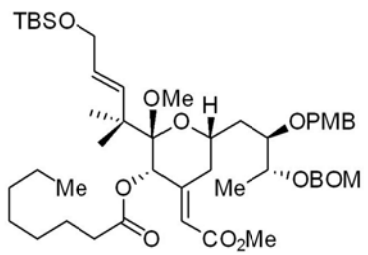


2.104 ^{1}H NMR (500 MHz, $CDCl_3$)

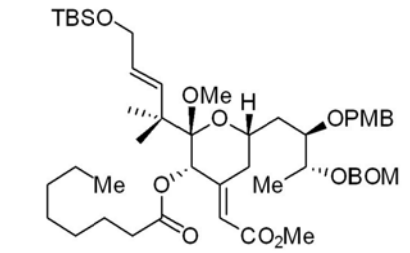


2.104 ^{13}C NMR (125 MHz, $CDCl_3$)

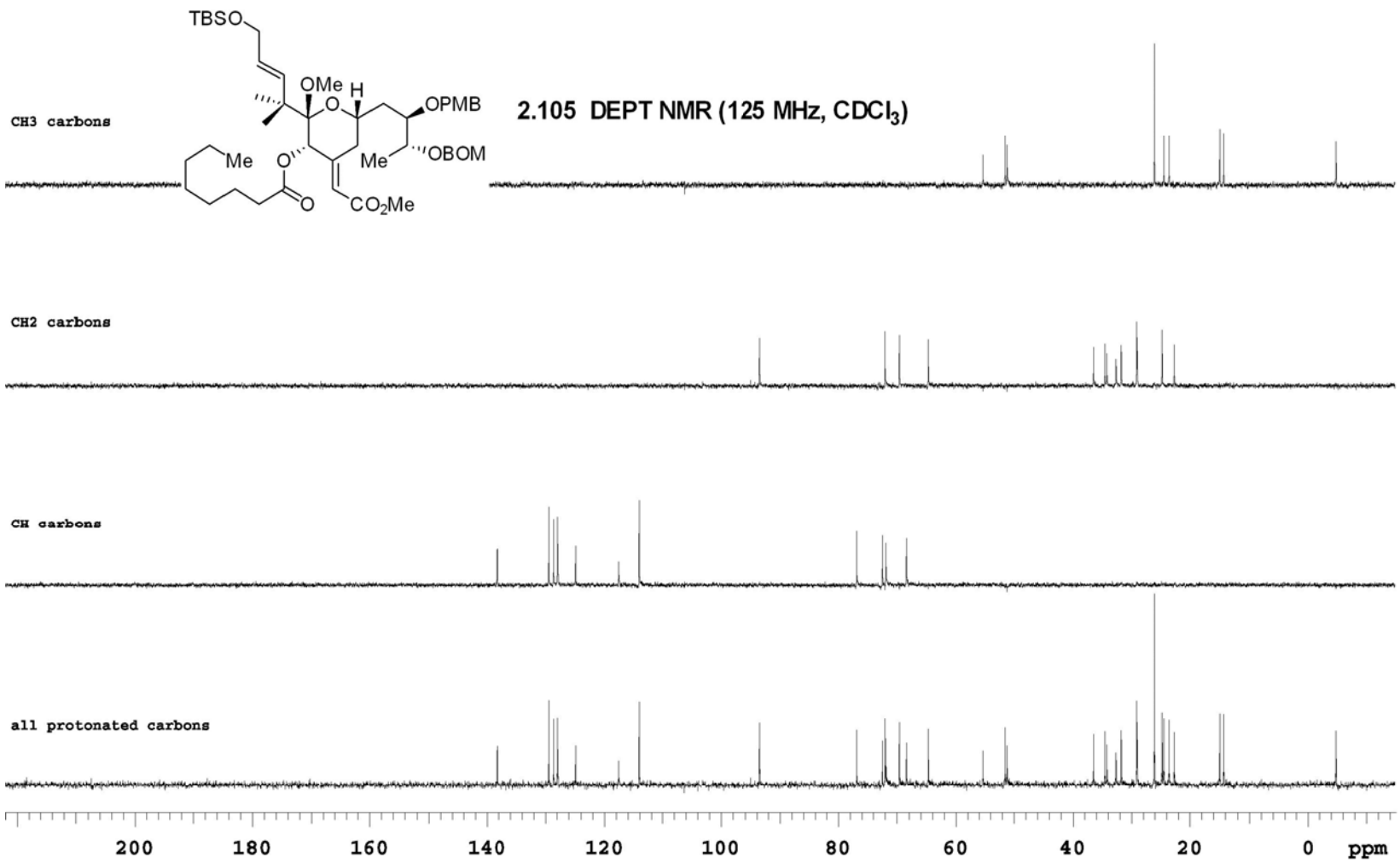

TBSO
OMe
H
O
OPMB
O
Me
OBOM
CO2Me
2.104 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

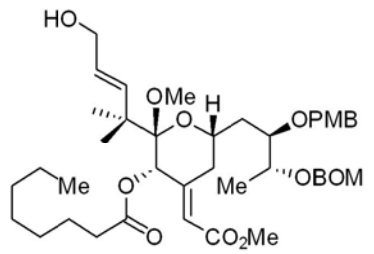


2.105 ^{1}H NMR (500 MHz, $CDCl_3$)

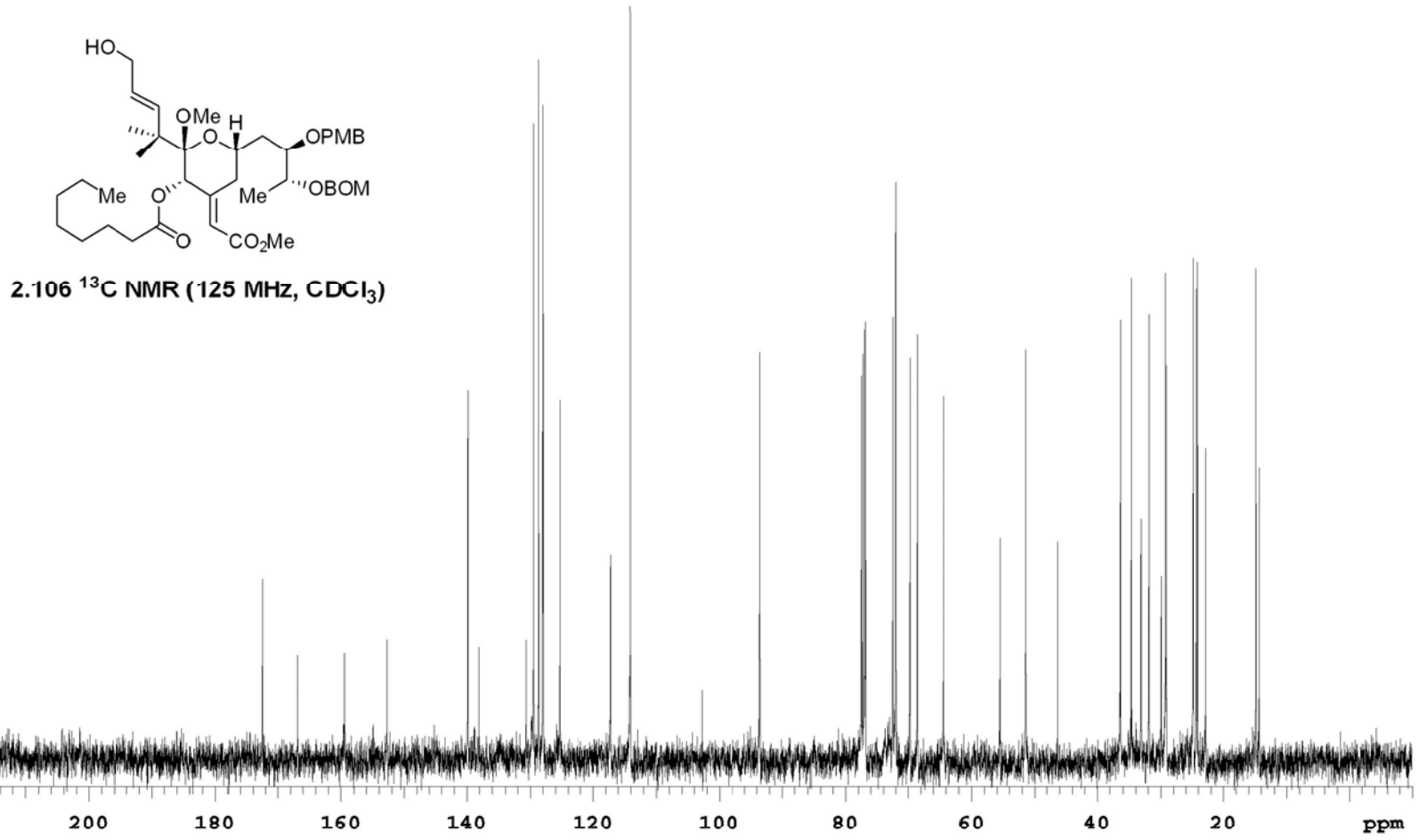


2.105 ^{13}C NMR (125 MHz, $CDCl_3$)

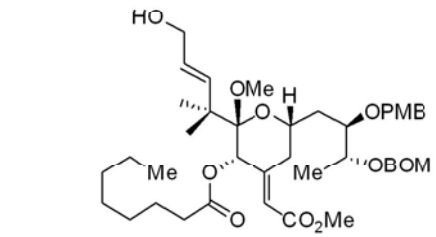

TBSO
OMe
H
OPMB
OBOM
Me
Me
O
O
O
CO2Me
2.105 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm



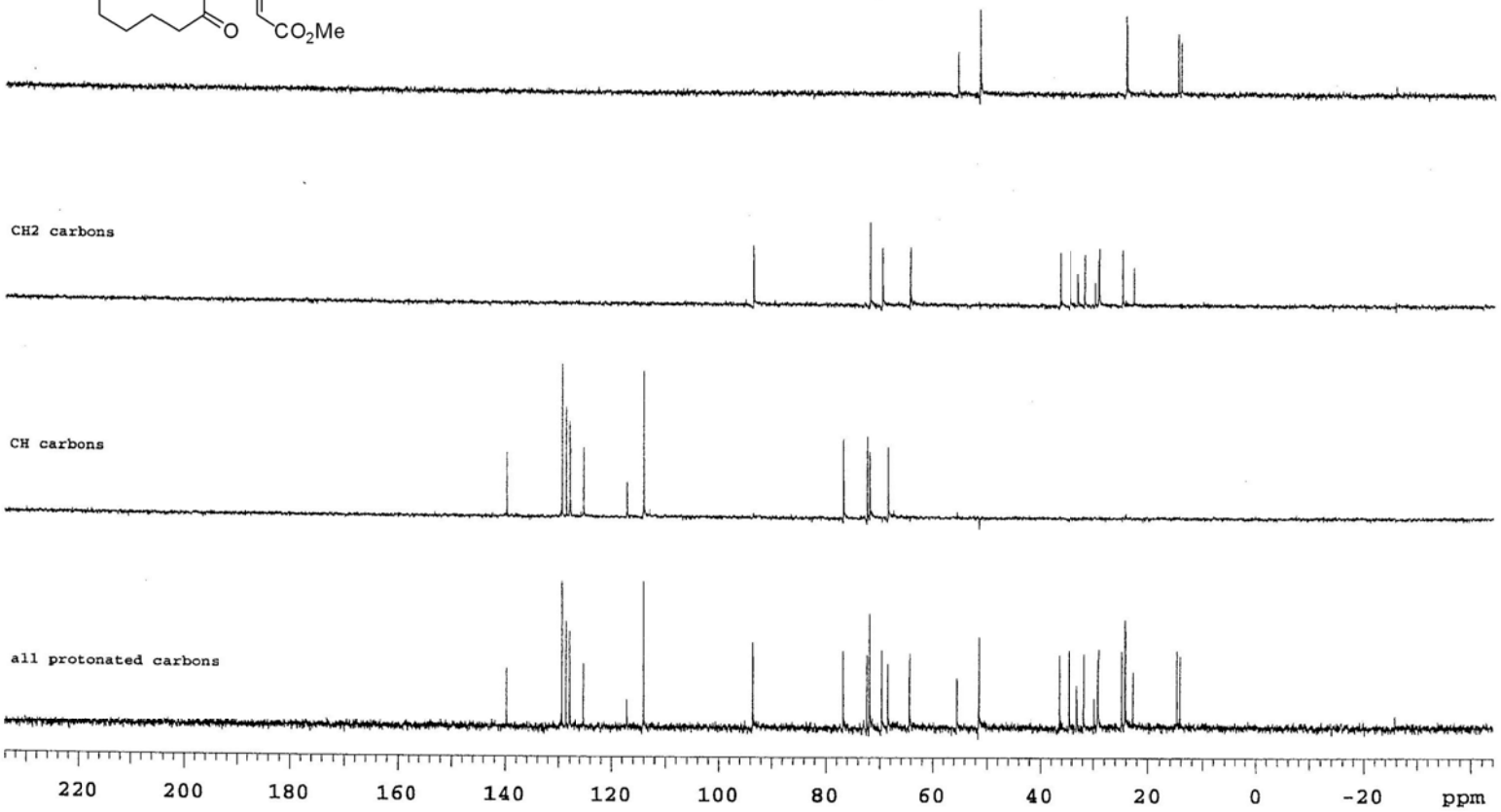
2.106 ^{1}H NMR (500 MHz, $CDCl_3$)

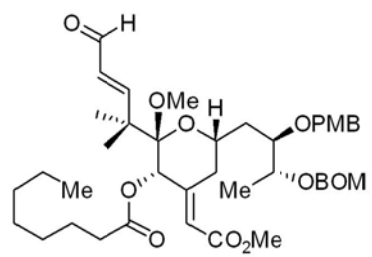


2.106 ^{13}C NMR (125 MHz, $CDCl_3$)

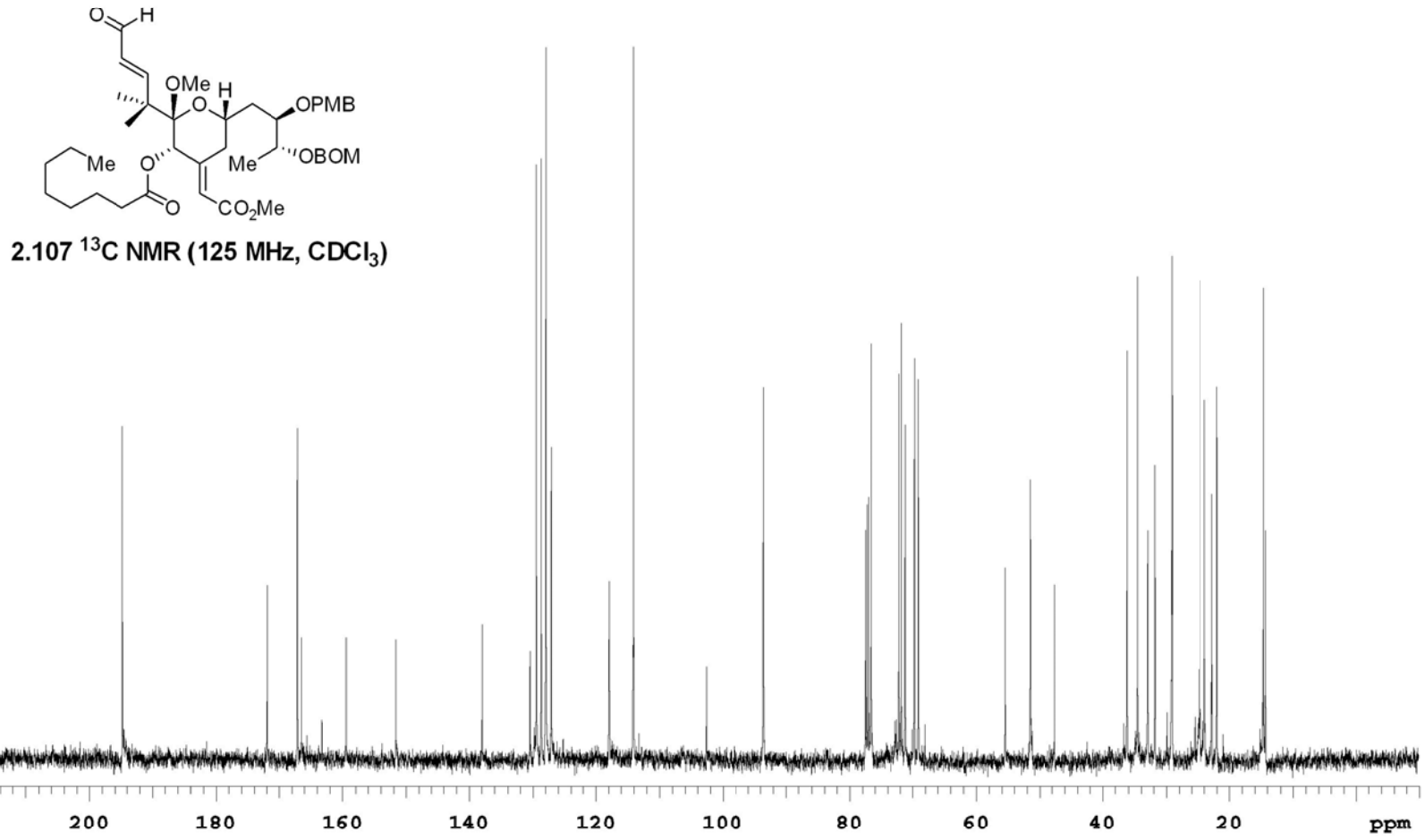


2.106 DEPT NMR (125 MHz, $CDCl_3$)

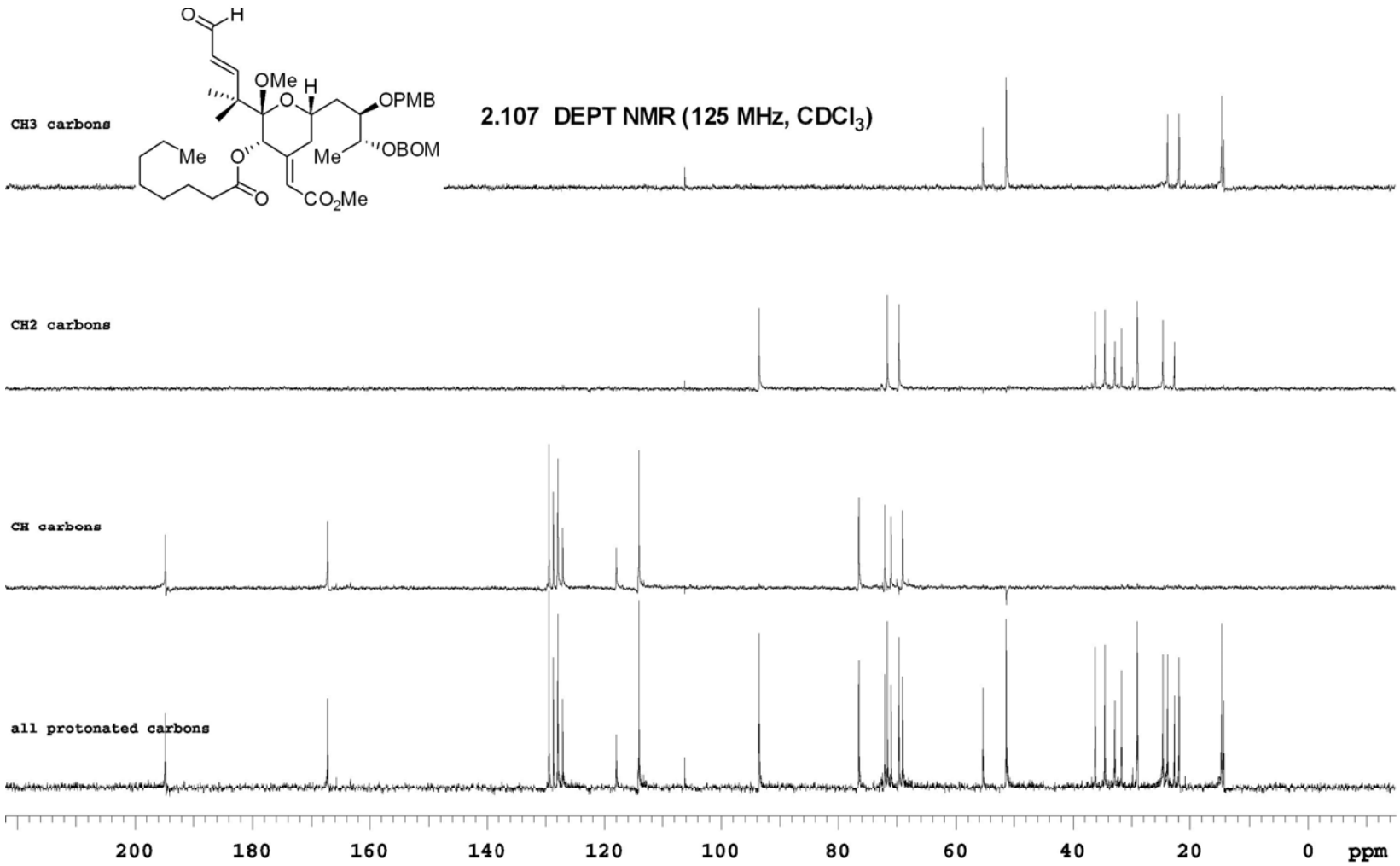


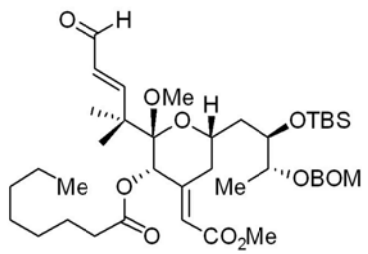


2.107 ^{1}H NMR (500 MHz, $CDCl_3$)

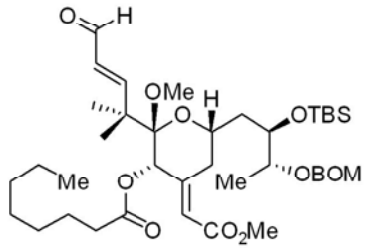


2.107 ^{13}C NMR (125 MHz, $CDCl_3$)

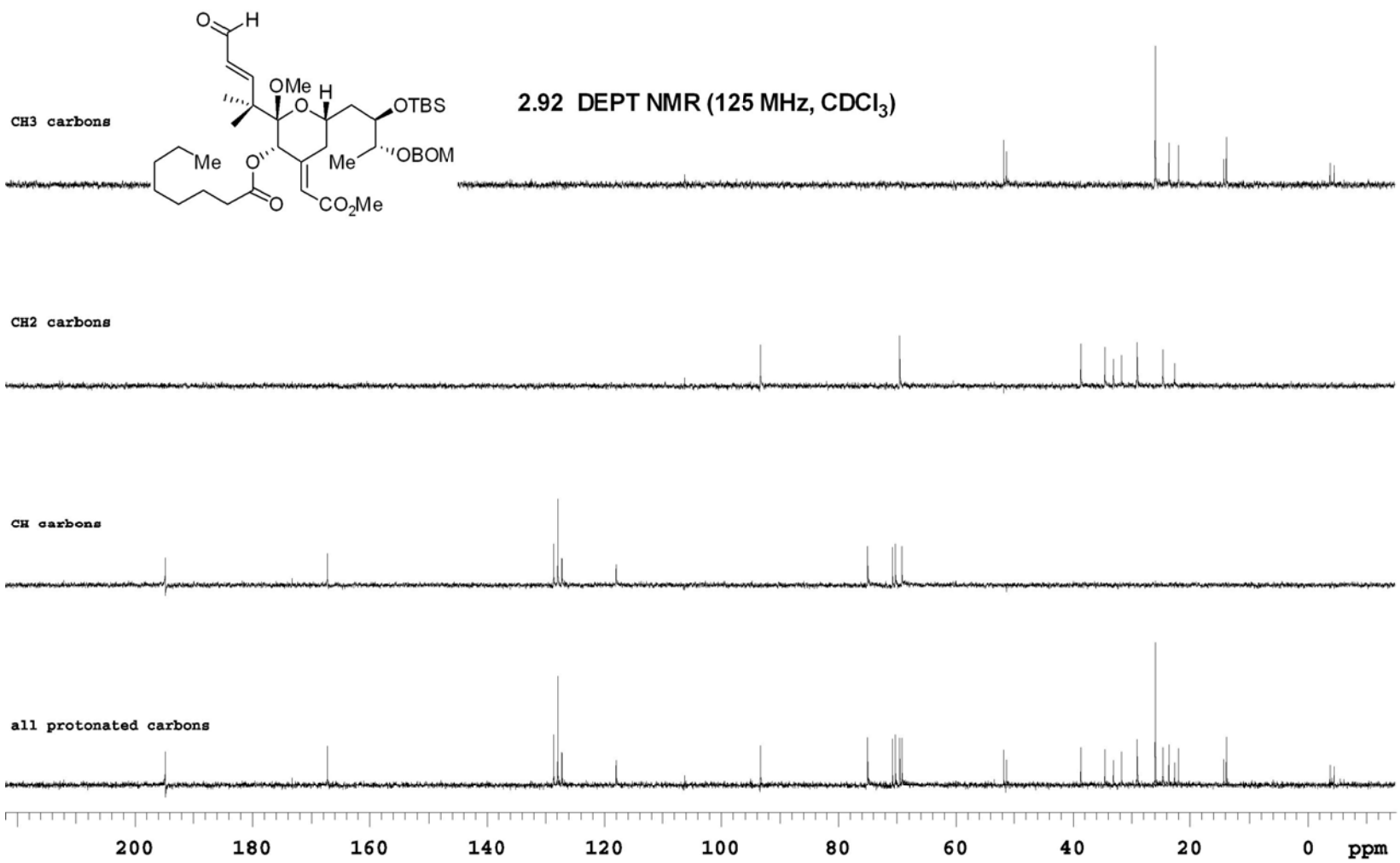

2.107 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OMe
H
OPMB
OBOM
Me
Me
CO2Me
200
180
160
140
120
100
80
60
40
20
0
ppm

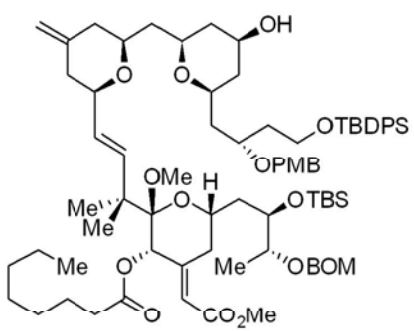


2.92 ^{1}H NMR (500 MHz, $CDCl_3$)

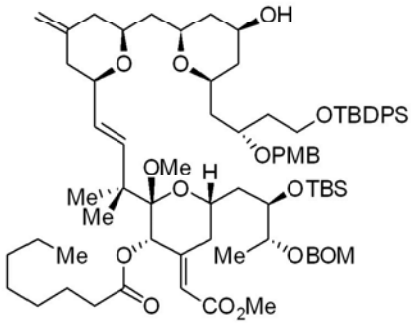


2.92 ^{13}C NMR (125 MHz, $CDCl_3$)

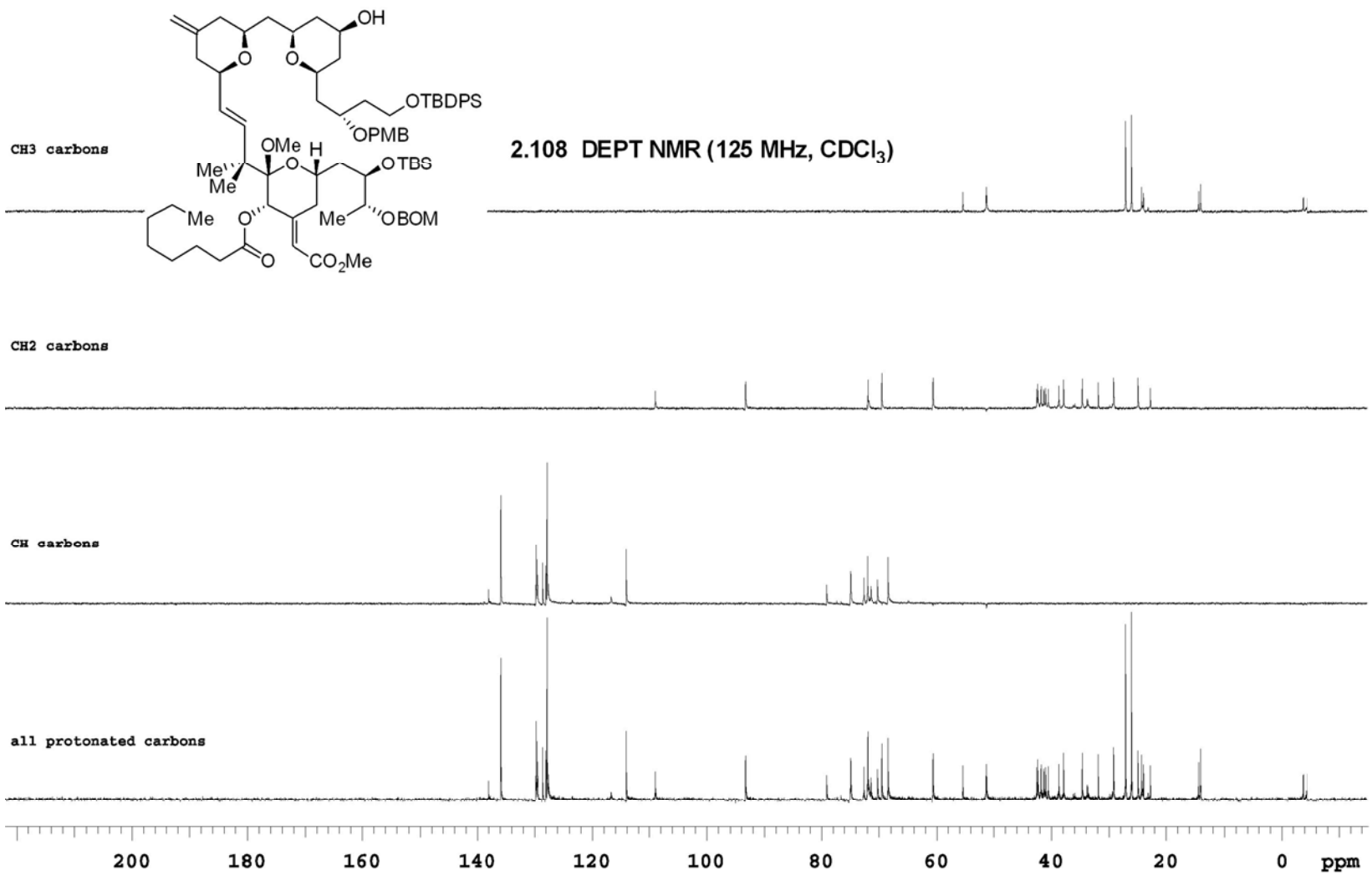

2.92 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OMe
H
OTBS
OBOM
Me
Me
CO2Me
200
180
160
140
120
100
80
60
40
20
0
ppm

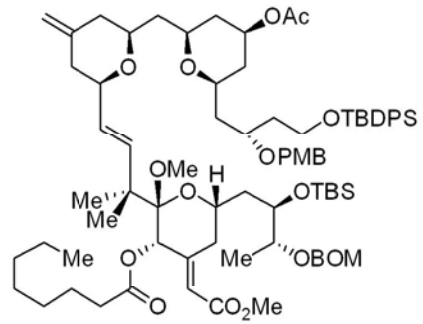


2.108 ^{1}H NMR (500 MHz, $CDCl_3$)

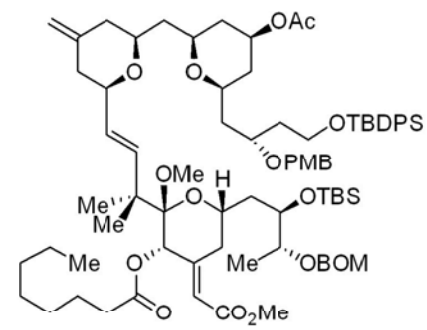


2.108 ^{13}C NMR (125 MHz, $CDCl_3$)

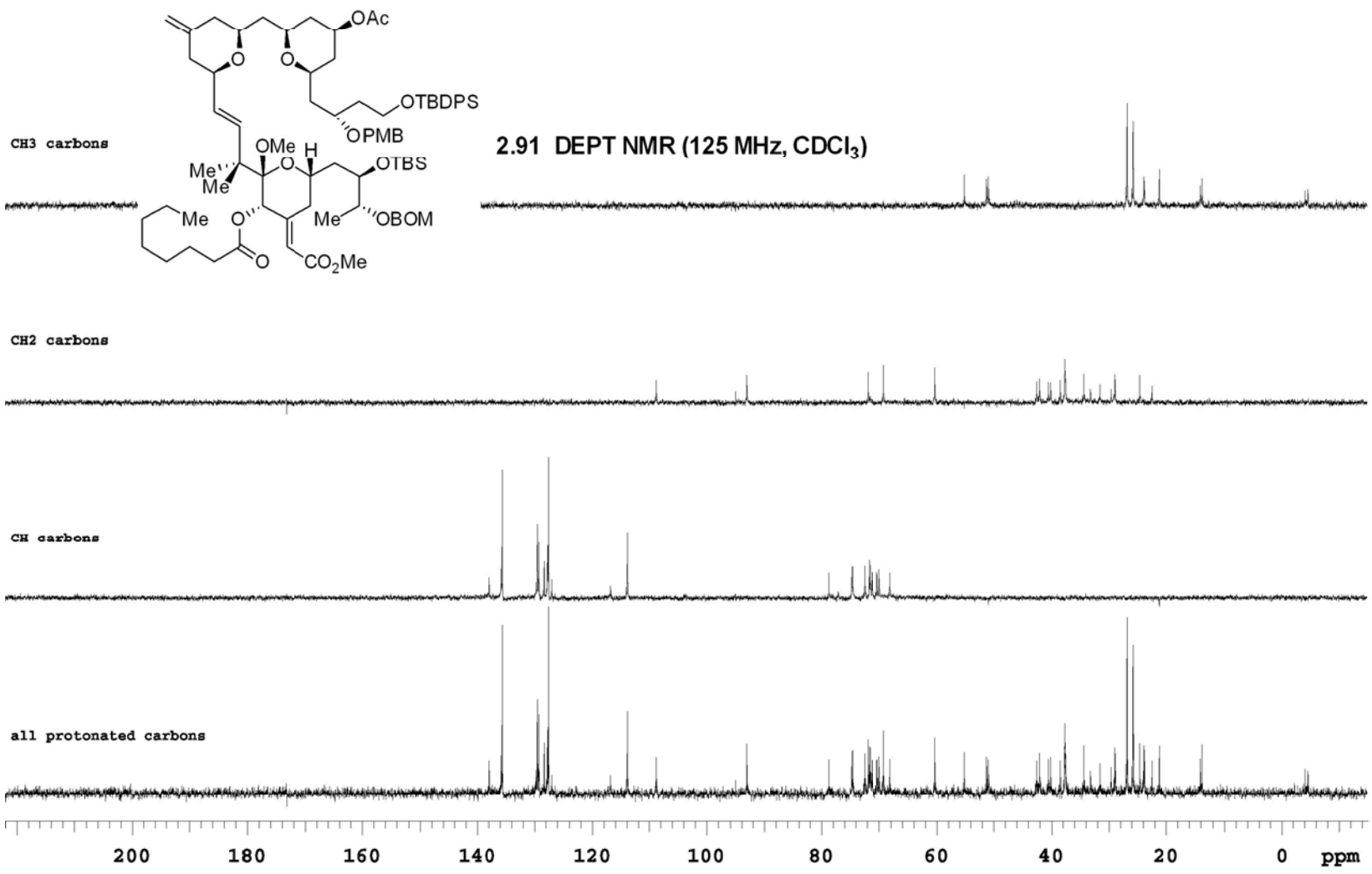

OH
OTBDPS
OPMB
OMe
H
OTBS
Me
Me
Me
O
Me
OBOM
O
O
CO2Me
CH3 carbons
2.108 DEPT NMR (125 MHz, CDCl3)
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

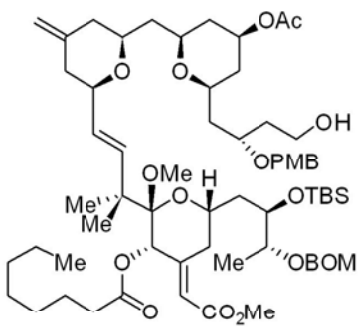


2.91 ^{1}H NMR (500 MHz, $CDCl_3$)

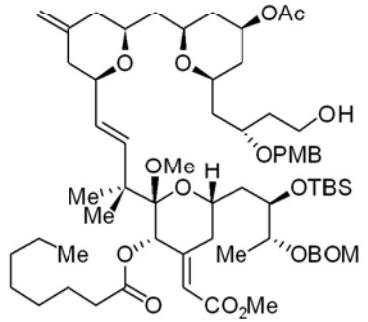


2.91 ^{13}C NMR (125 MHz, $CDCl_3$)

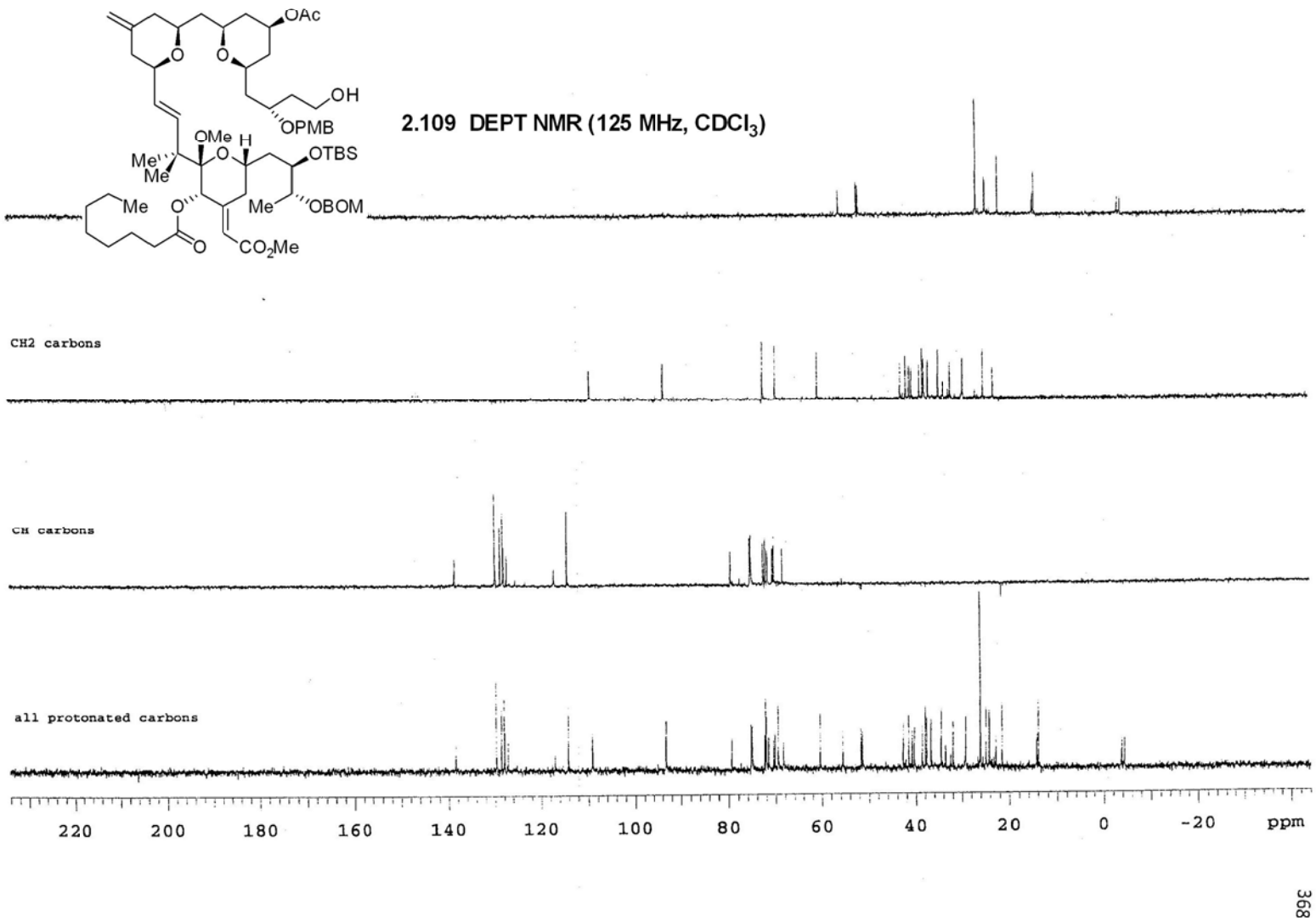

OAc
OTBDPS
OPMB
OMe
H
OTBS
Me
Me
Me
O
Me
OBOM
O
O
CO_2Me
CH3 carbons
2.91 DEPT NMR (125 MHz, $CDCl_3$)
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

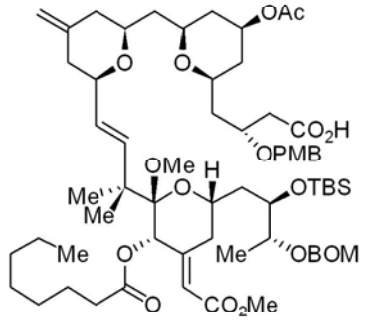


2.109 ^{1}H NMR (500 MHz, $CDCl_3$)

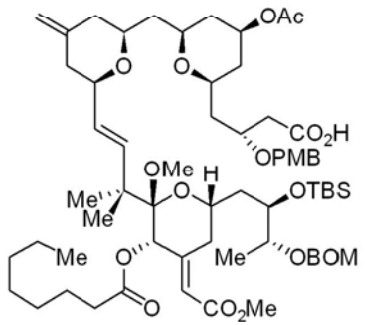


2.109 ^{13}C NMR (125 MHz, $CDCl_3$)

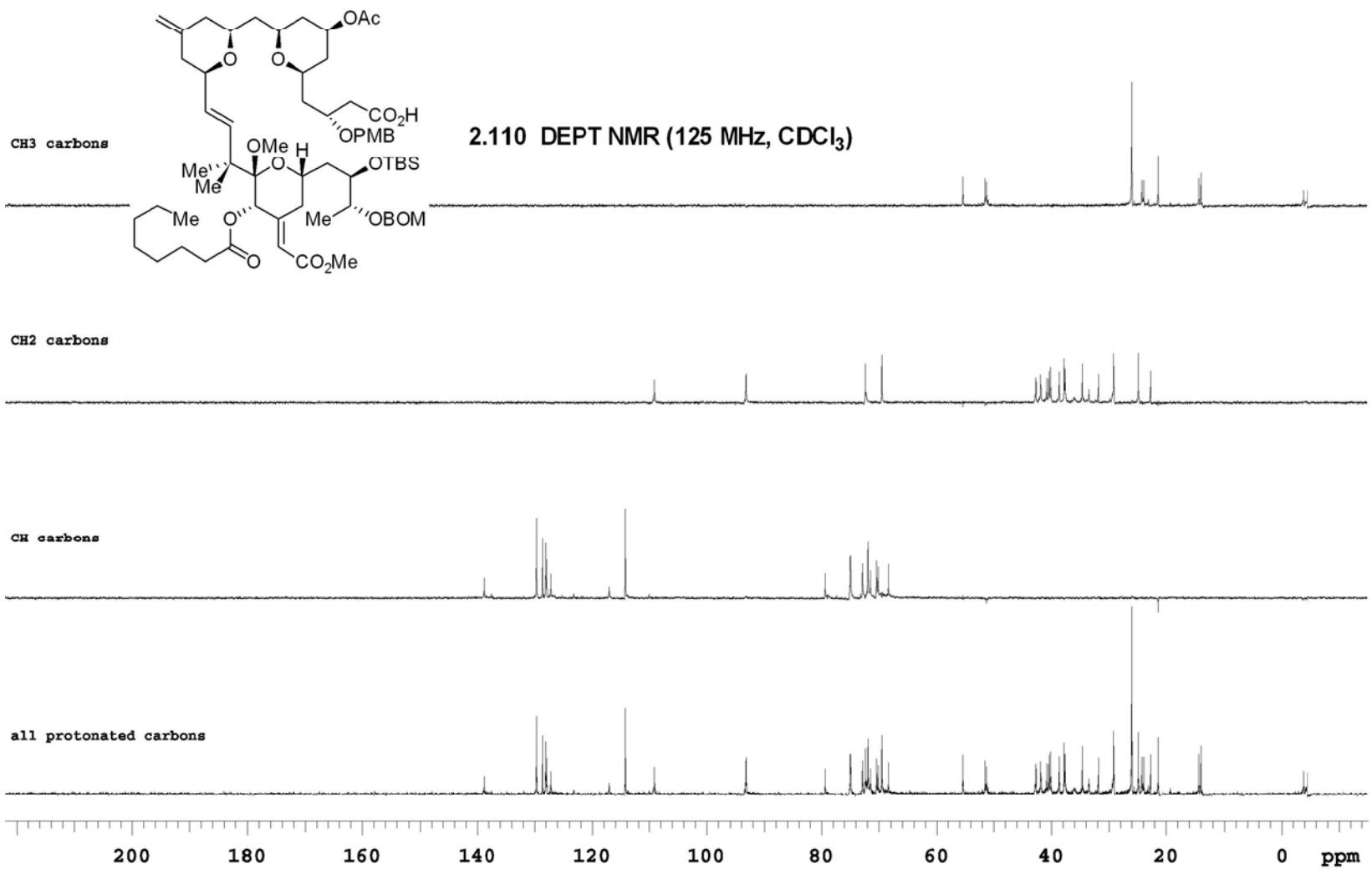

OAc
OH
OPMB
OMe
H
OTBS
Me
Me
Me
O
Me
OBOM
O
CO2Me
2.109 DEPT NMR (125 MHz, CDCl3)
CH2 carbons
CH carbons
all protonated carbons
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

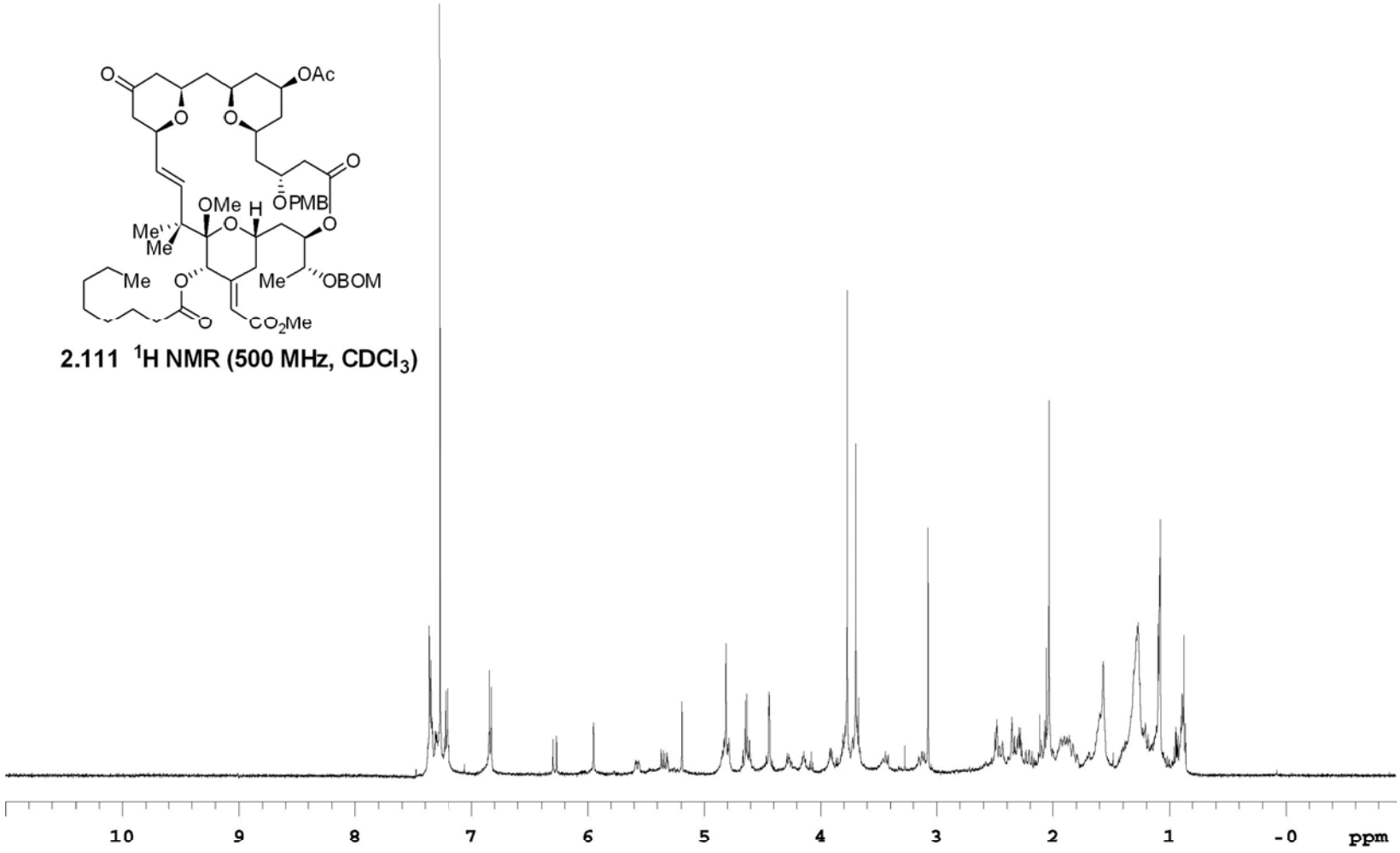


2.110 ^{1}H NMR (500 MHz, $CDCl_3$)

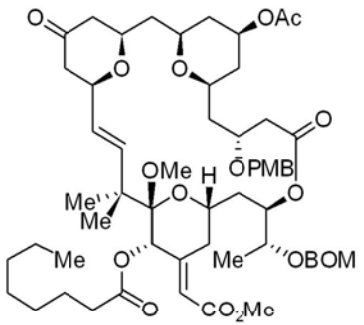


2.110 ^{13}C NMR (125 MHz, $CDCl_3$)

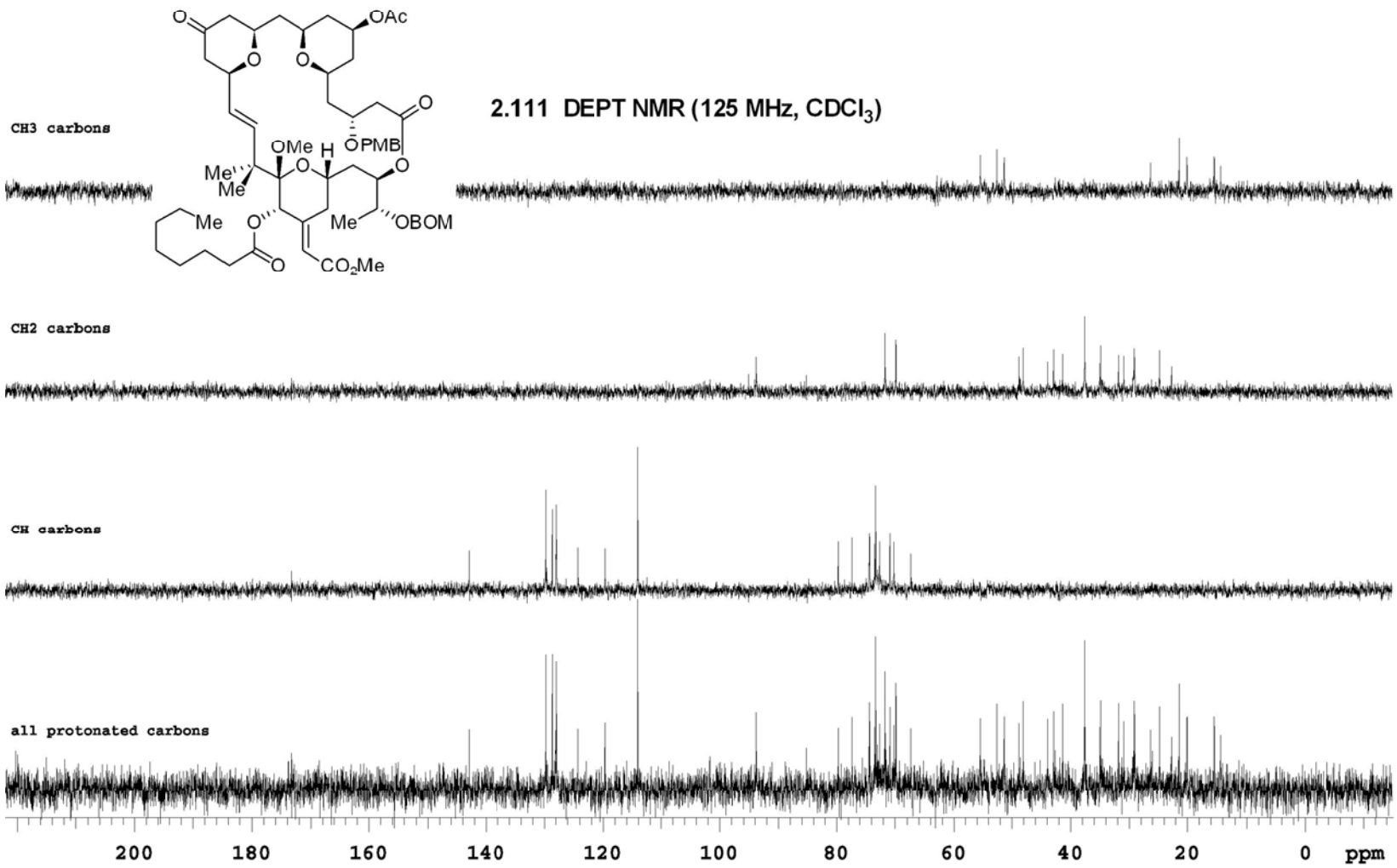

OAc
O
O
CO2H
OPMB
OMe
H
O
OTBS
Me
Me
Me
O
Me
OBOM
O
CO2Me
CH3 carbons
2.110 DEPT NMR (125 MHz, CDCl3)
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

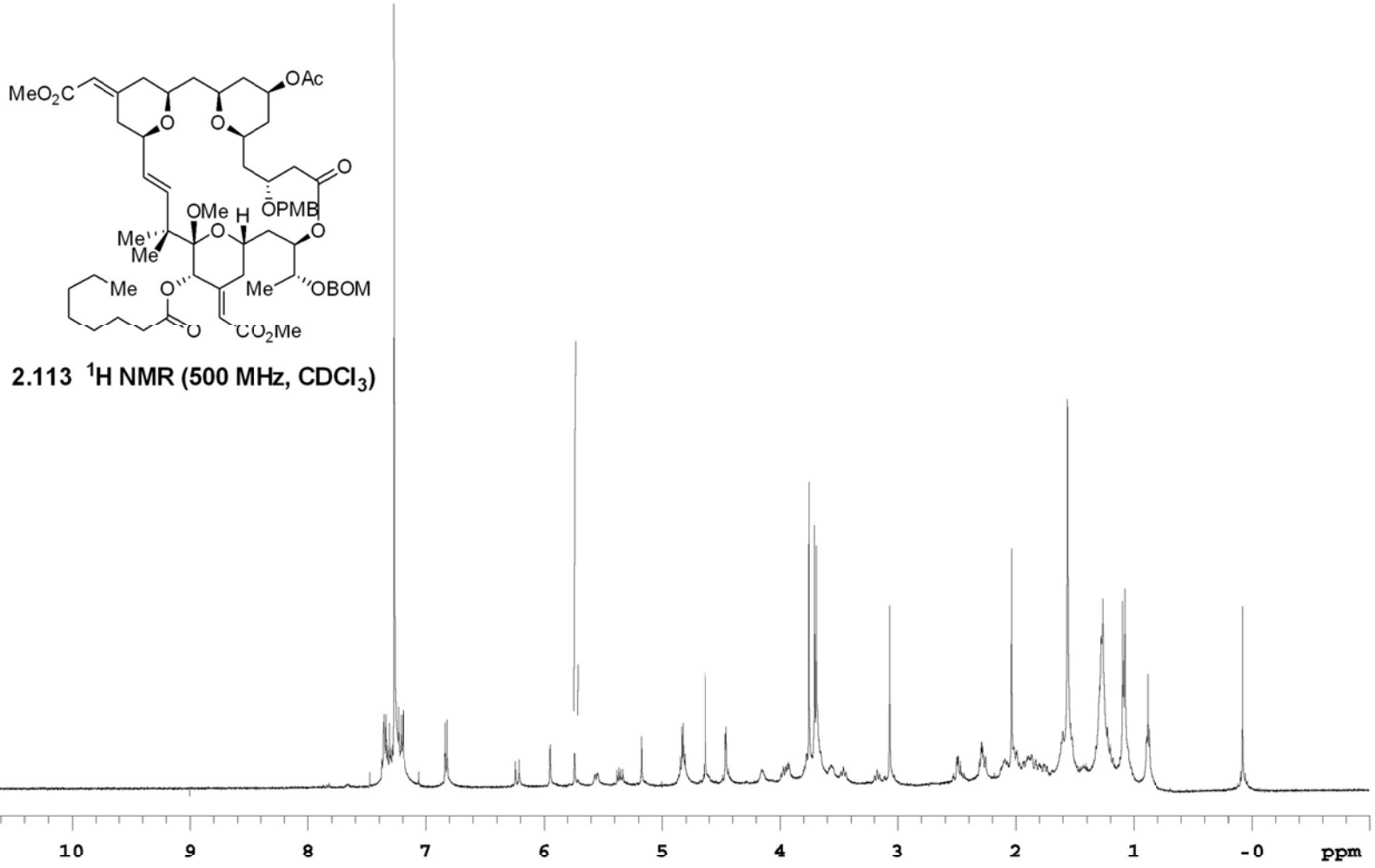


2.111 ^{1}H NMR (500 MHz, $CDCl_3$)

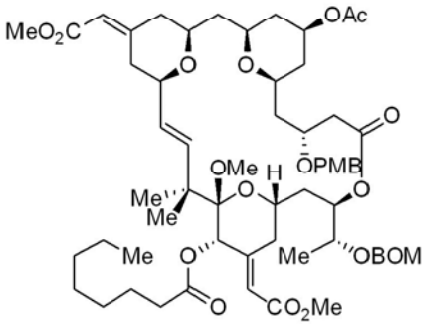


2.111 ^{13}C NMR (125 MHz, $CDCl_3$)

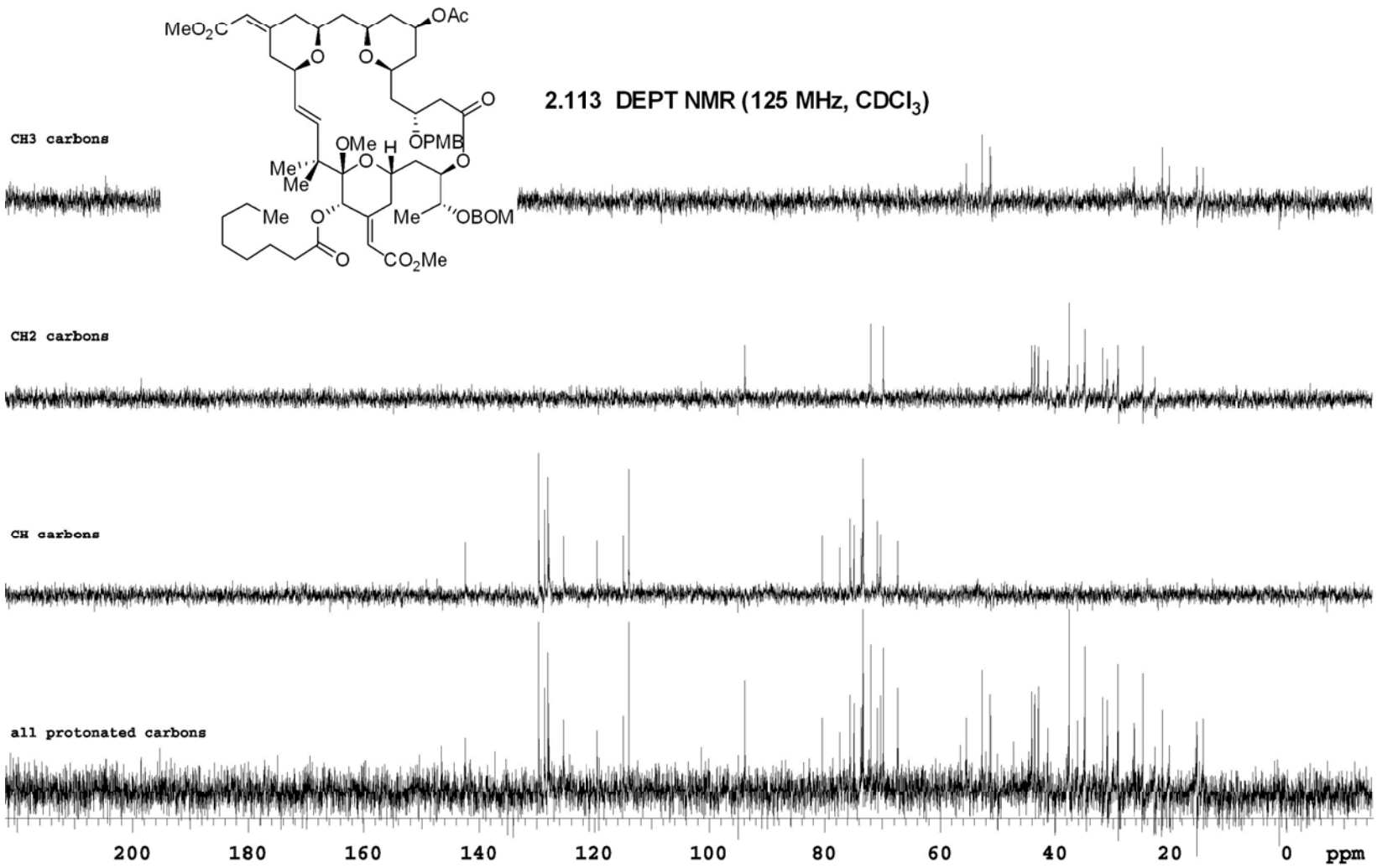

2.111 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OAc
OMe
H
OPMB
Me
Me
Me
OBOM
CO2Me
200
180
160
140
120
100
80
60
40
20
0
ppm

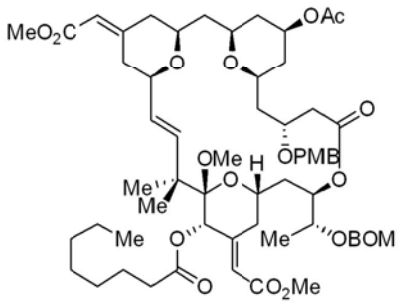


2.113 ^{1}H NMR (500 MHz, $CDCl_3$)

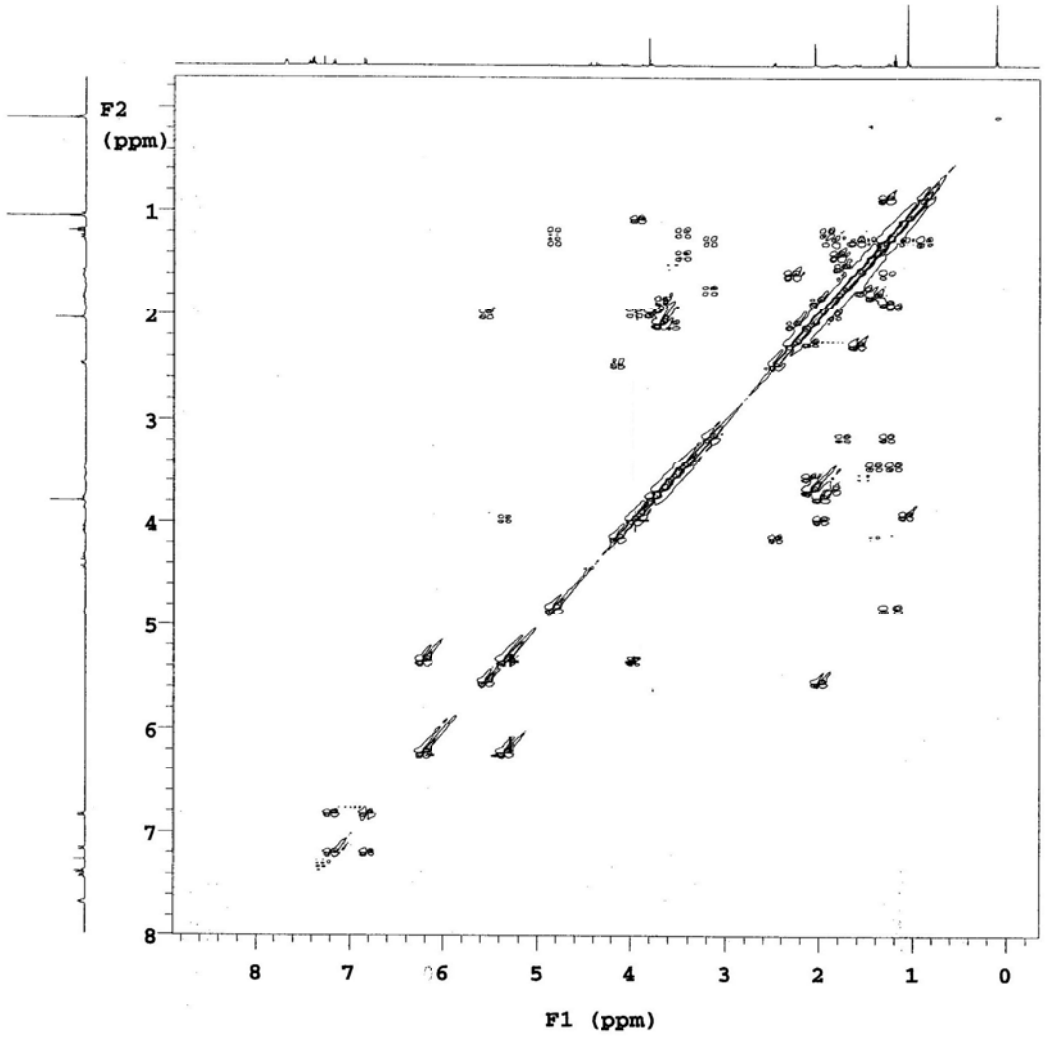


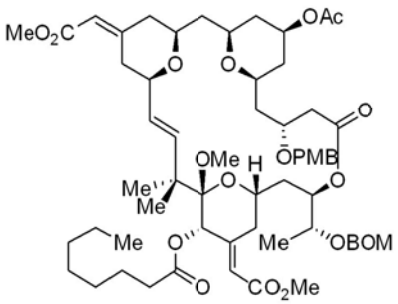
2.113 ^{13}C NMR (125 MHz, $CDCl_3$)

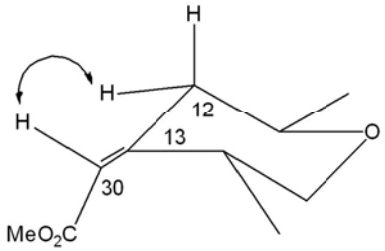

MeO2C
OAc
O
O
O
OMe
H
OPMB
O
Me
Me
Me
O
Me
OBOM
O
O
CO2Me
2.113 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm



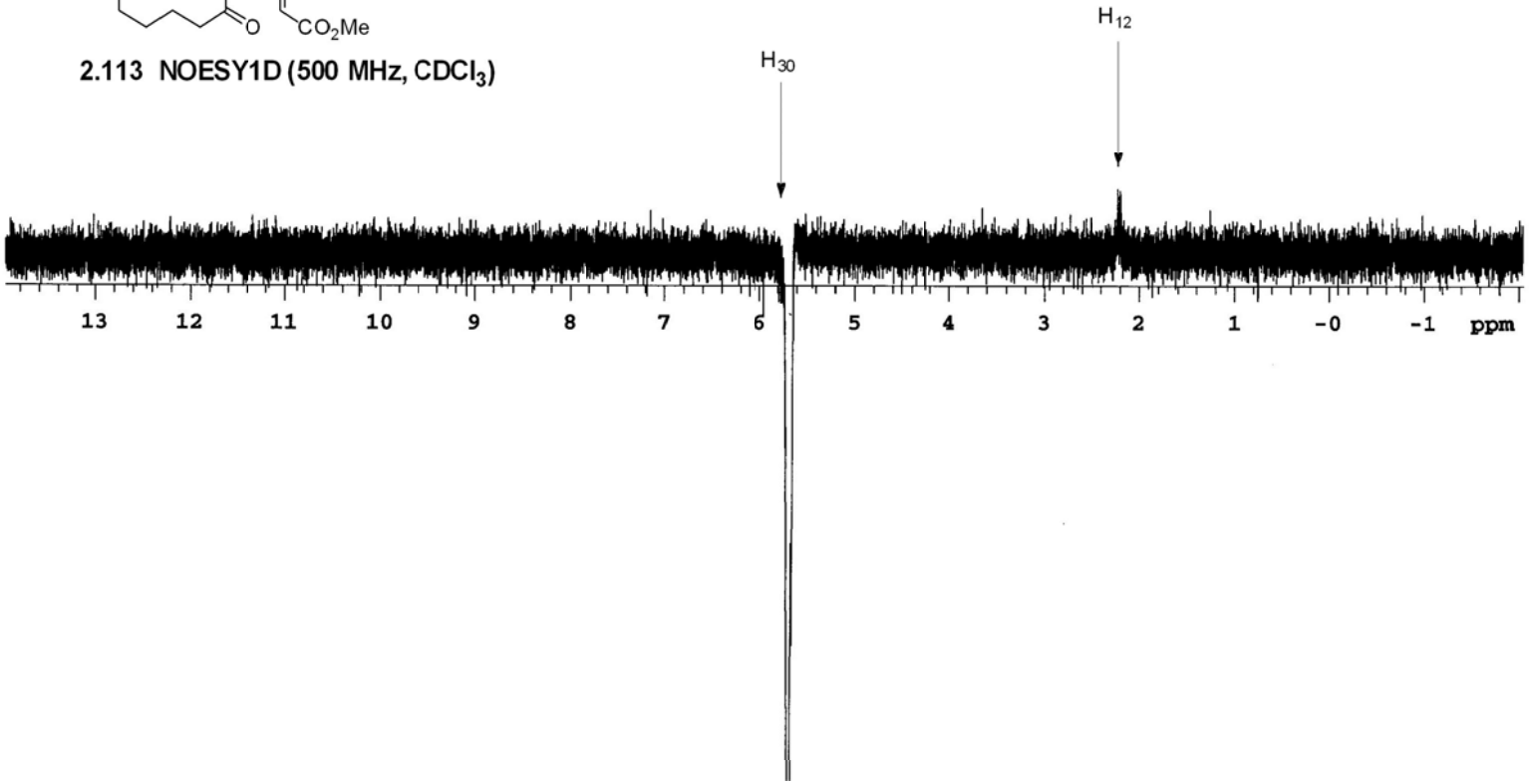
2.113 gCOSY (500 MHz, $CDCl_3$)

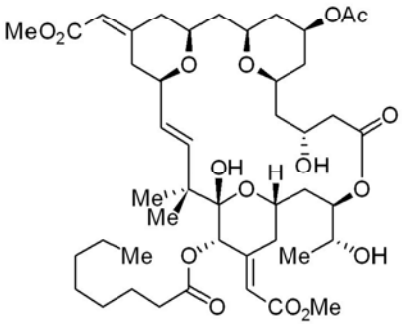




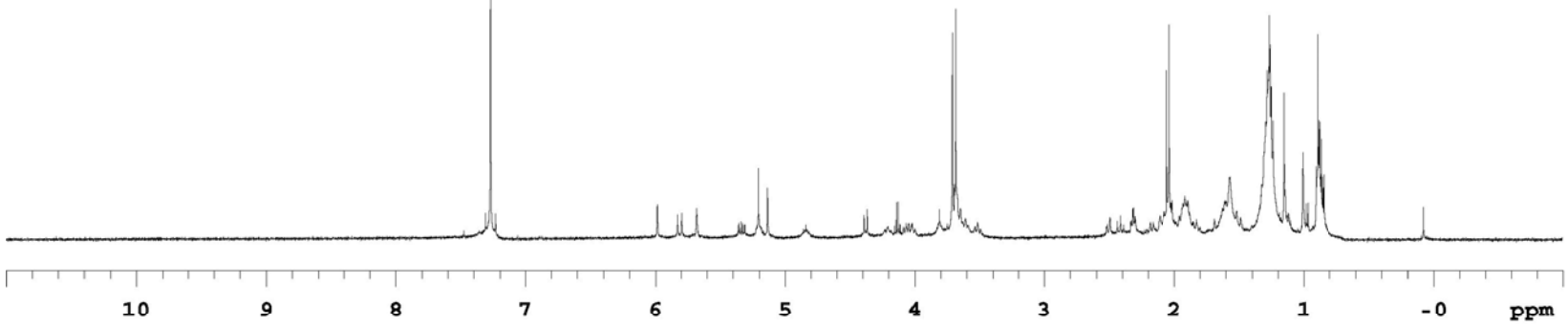


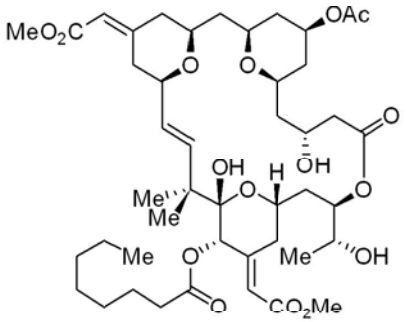
2.113 NOESY1D (500 MHz, $CDCl_3$)



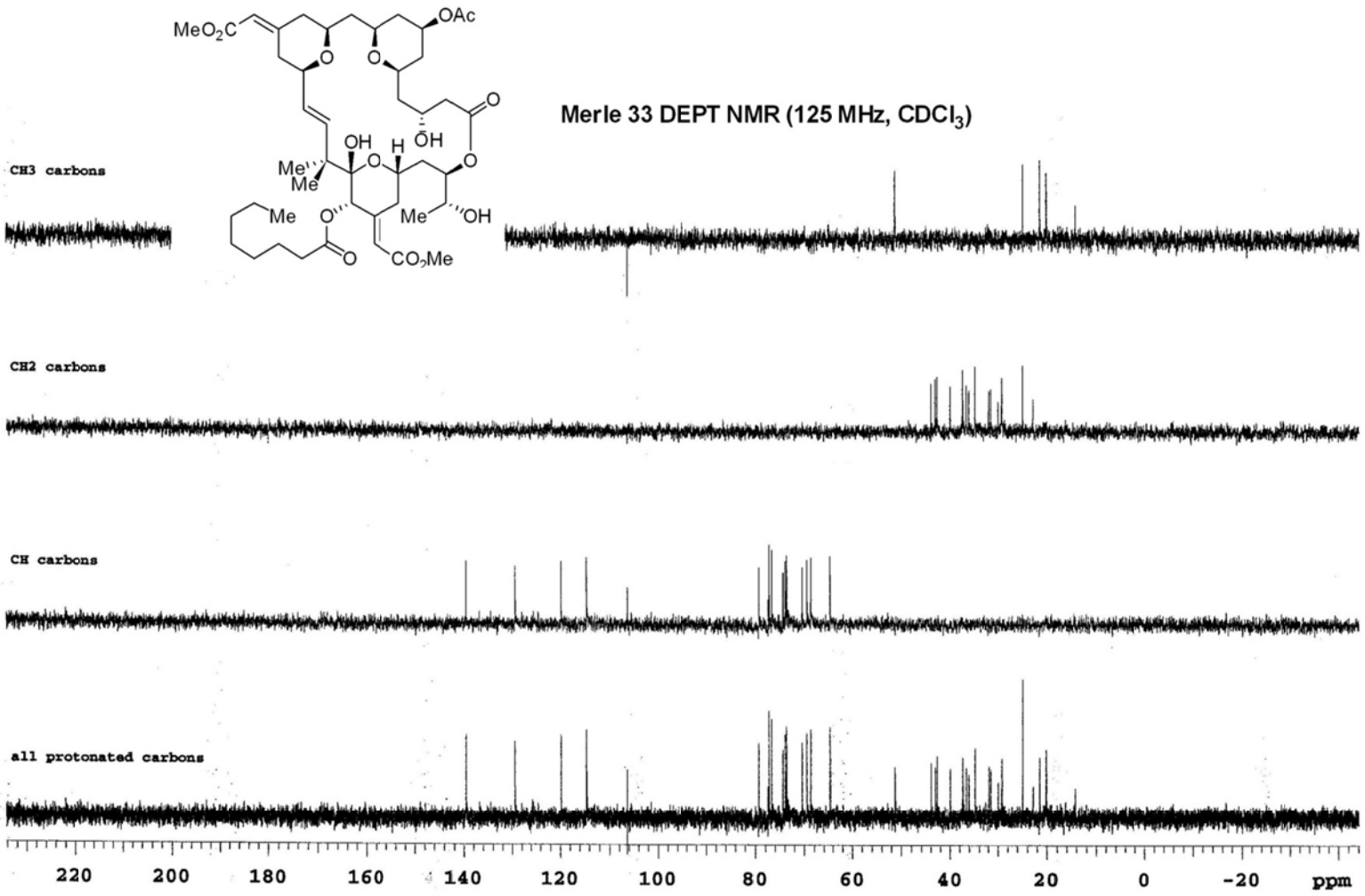


Merle 33 ^{1}H NMR (500 MHz, $CDCl_3$)



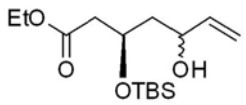


Merle 33 ^{13}C NMR (125 MHz, $CDCl_3$)

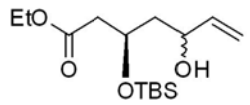

Merle 33 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
MeO2C
OAc
OH
H
OH
Me
Me
Me
Me
OH
CO2Me
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

APPENDIX B

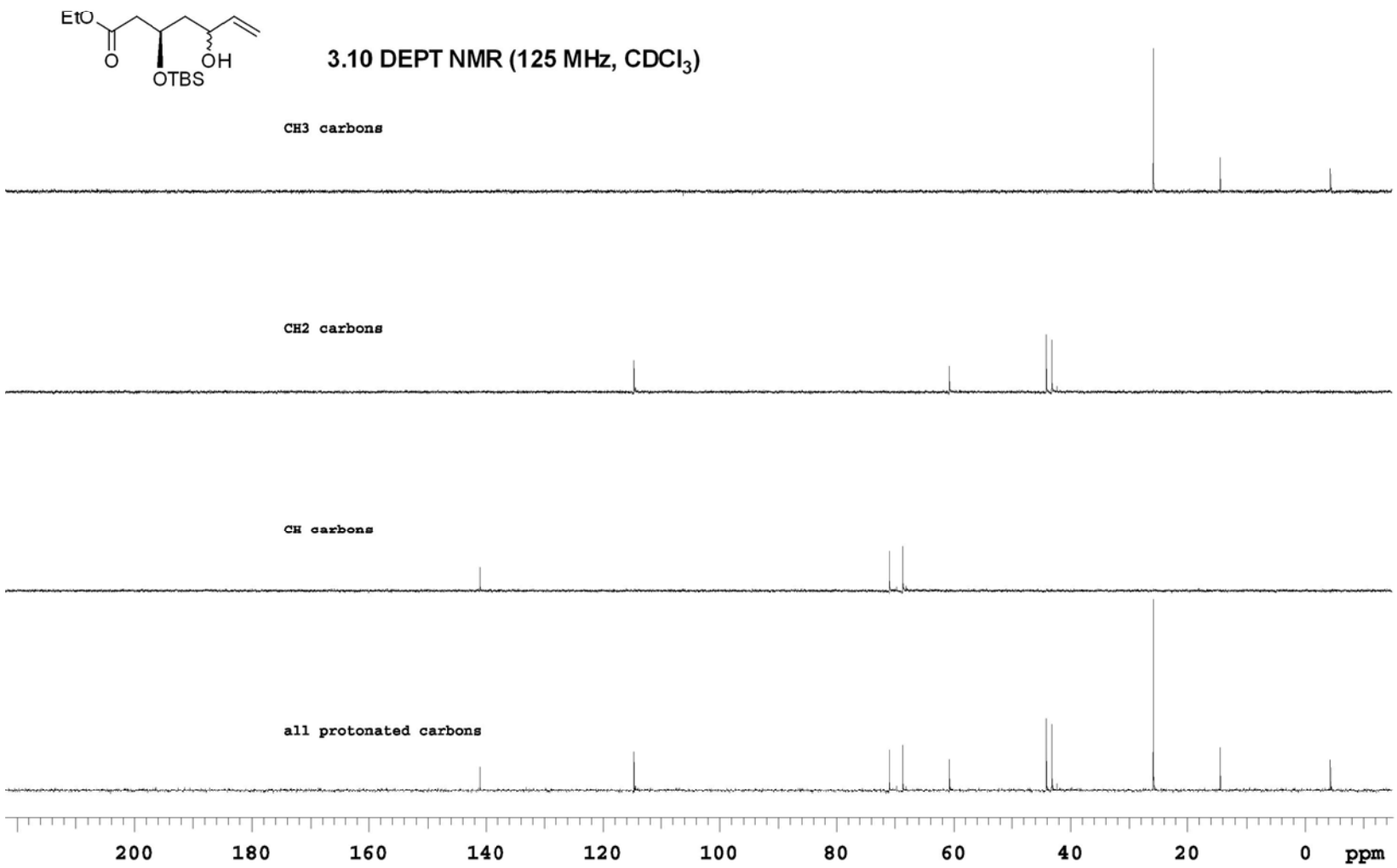
NMR SPECTRA OF CHAPTER 3

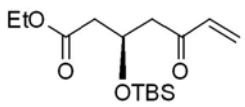


3.10 ^{1}H NMR (500 MHz, $CDCl_3$)

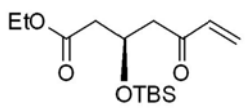


3.10 ^{13}C NMR (125 MHz, $CDCl_3$)

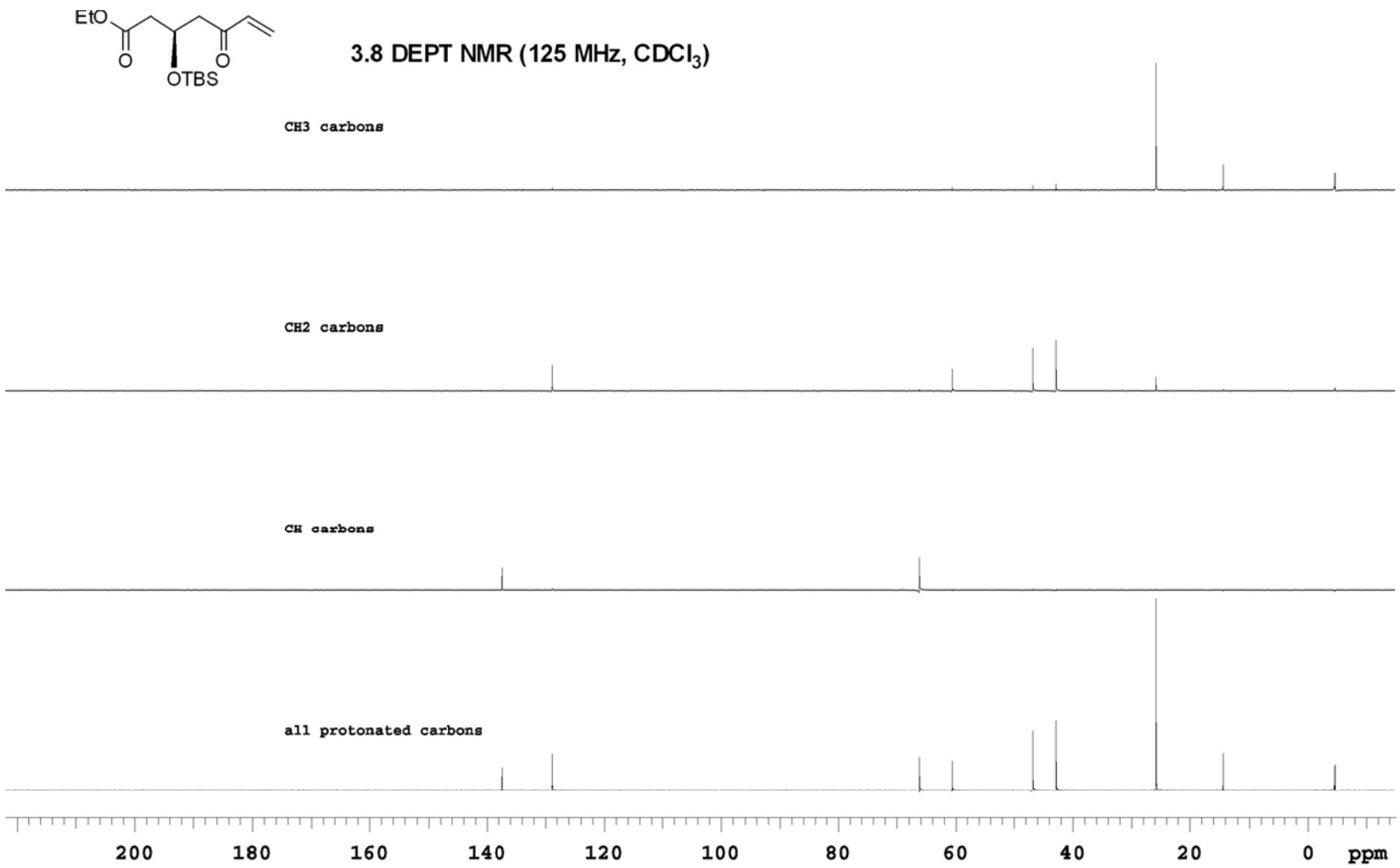

EtO
O
OH
OTBS
3.10 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

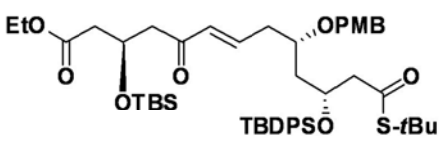


3.8 ^{1}H NMR (500 MHz, $CDCl_3$)

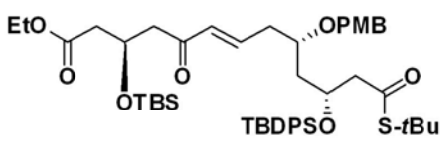


3.8 ^{13}C NMR (125 MHz, $CDCl_3$)

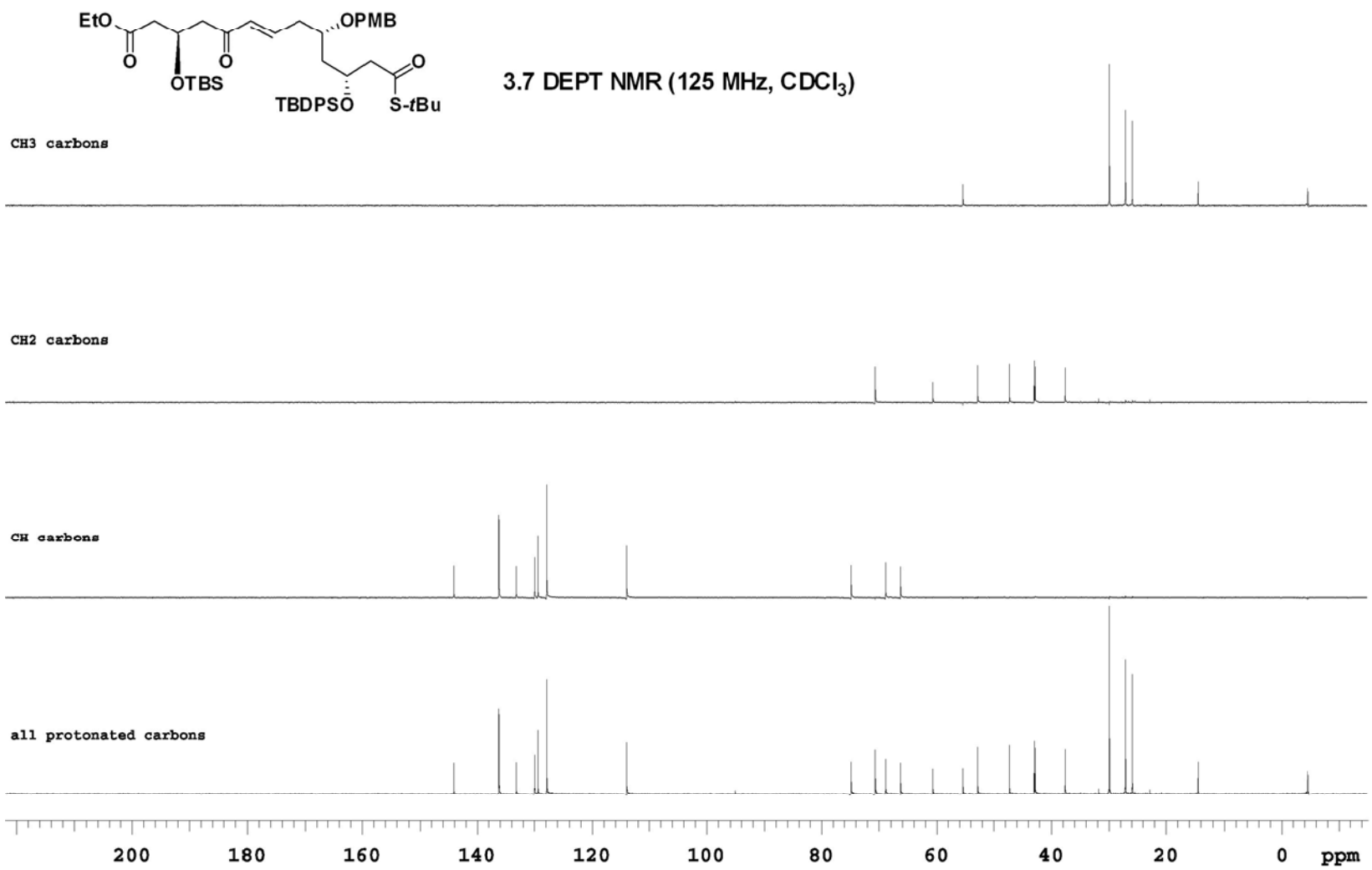

EtO
O
O
OTBS
3.8 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

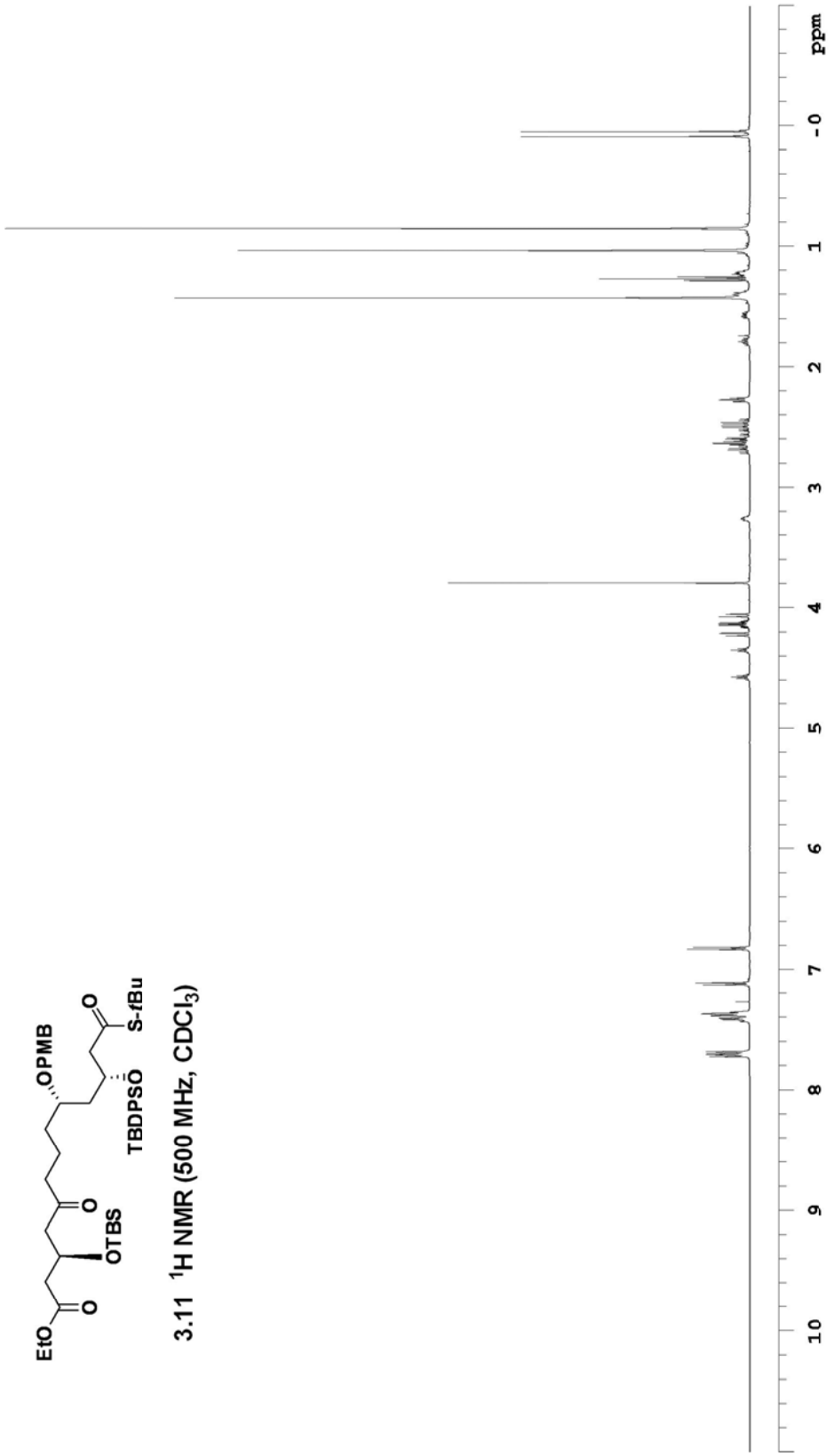


3.7 ^{1}H NMR (500 MHz, $CDCl_3$)

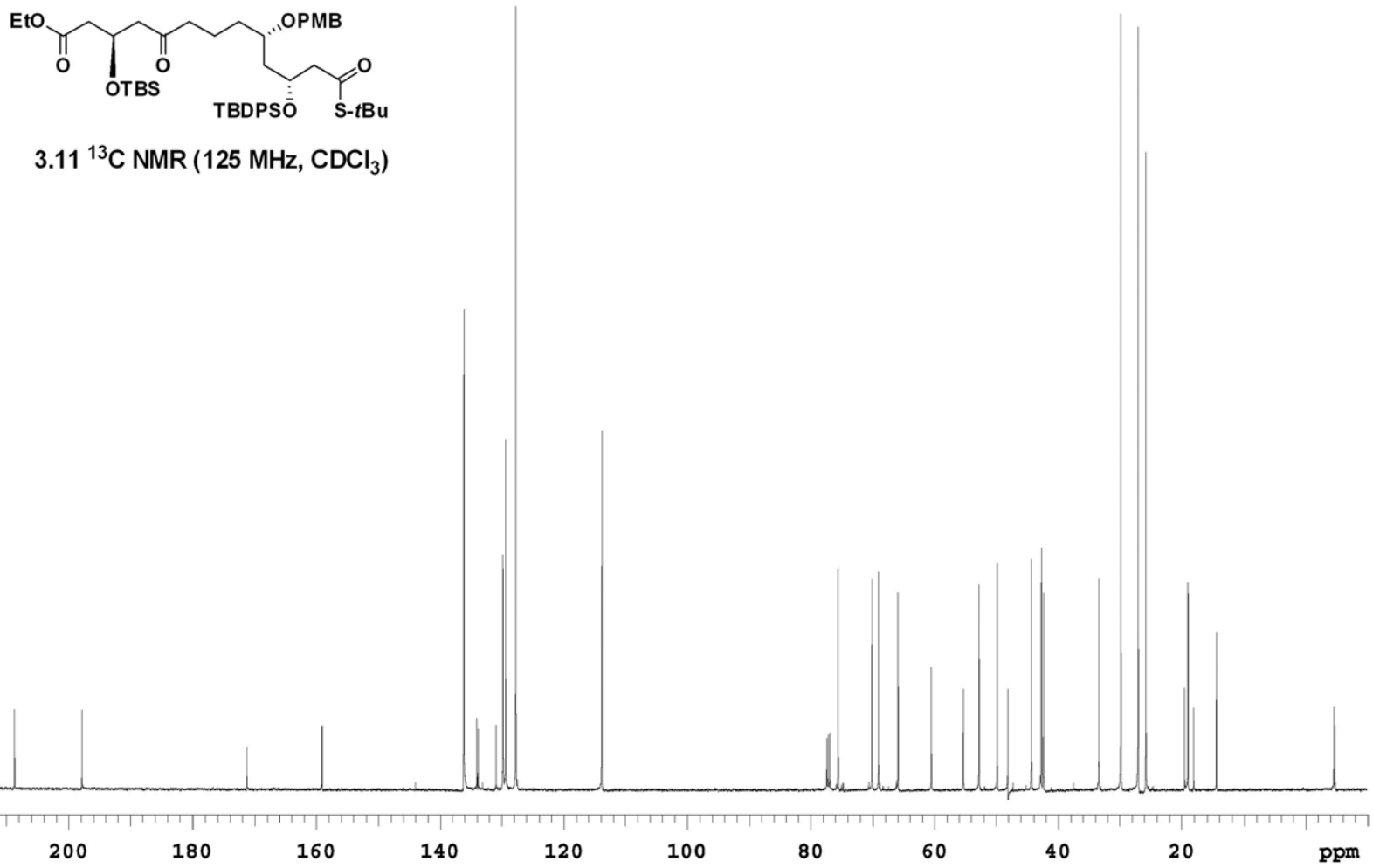


3.7 ^{13}C NMR (125 MHz, $CDCl_3$)

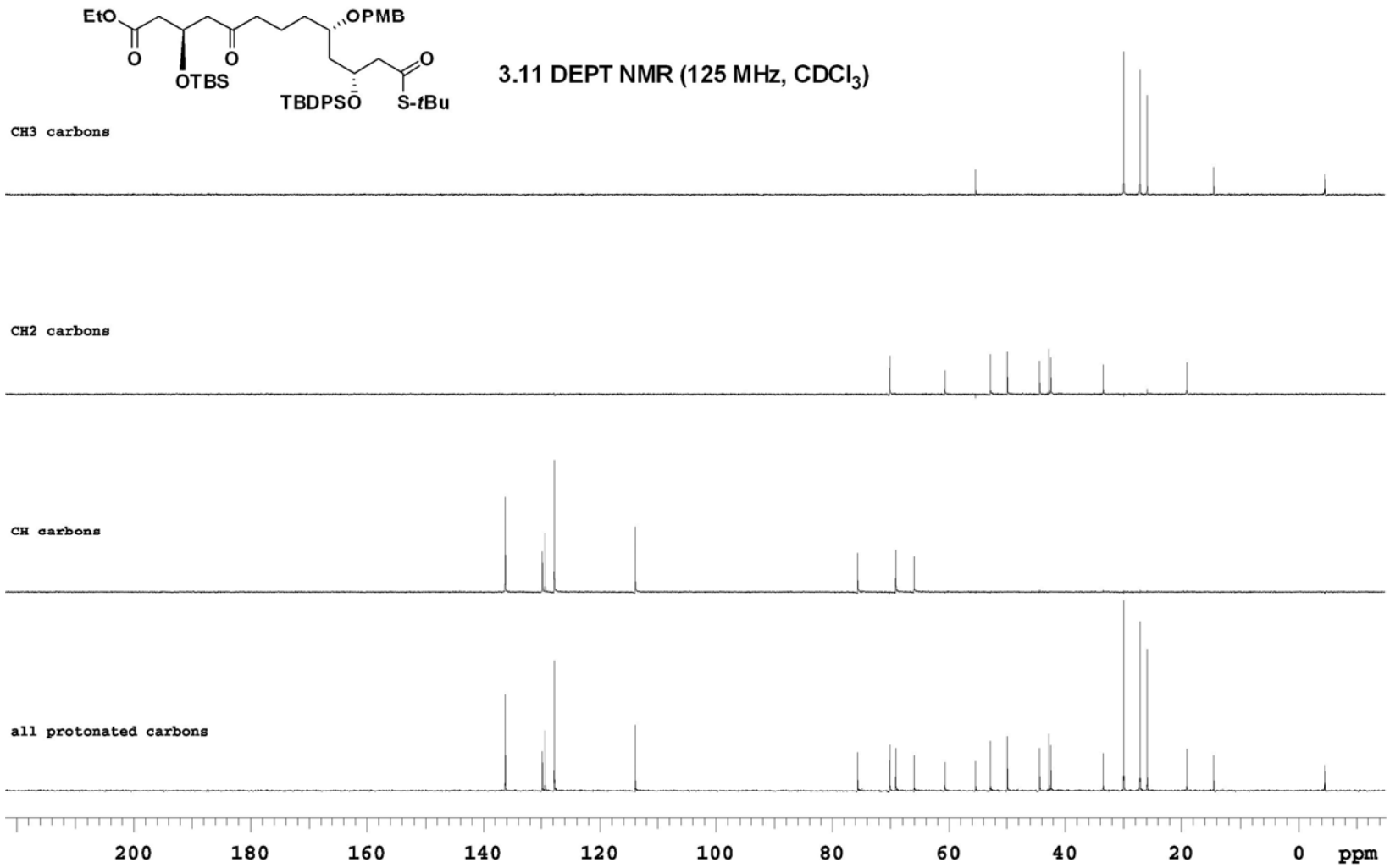

EtO
O
OTBS
O
OPMB
TBDPSO
O
S-tBu
3.7 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

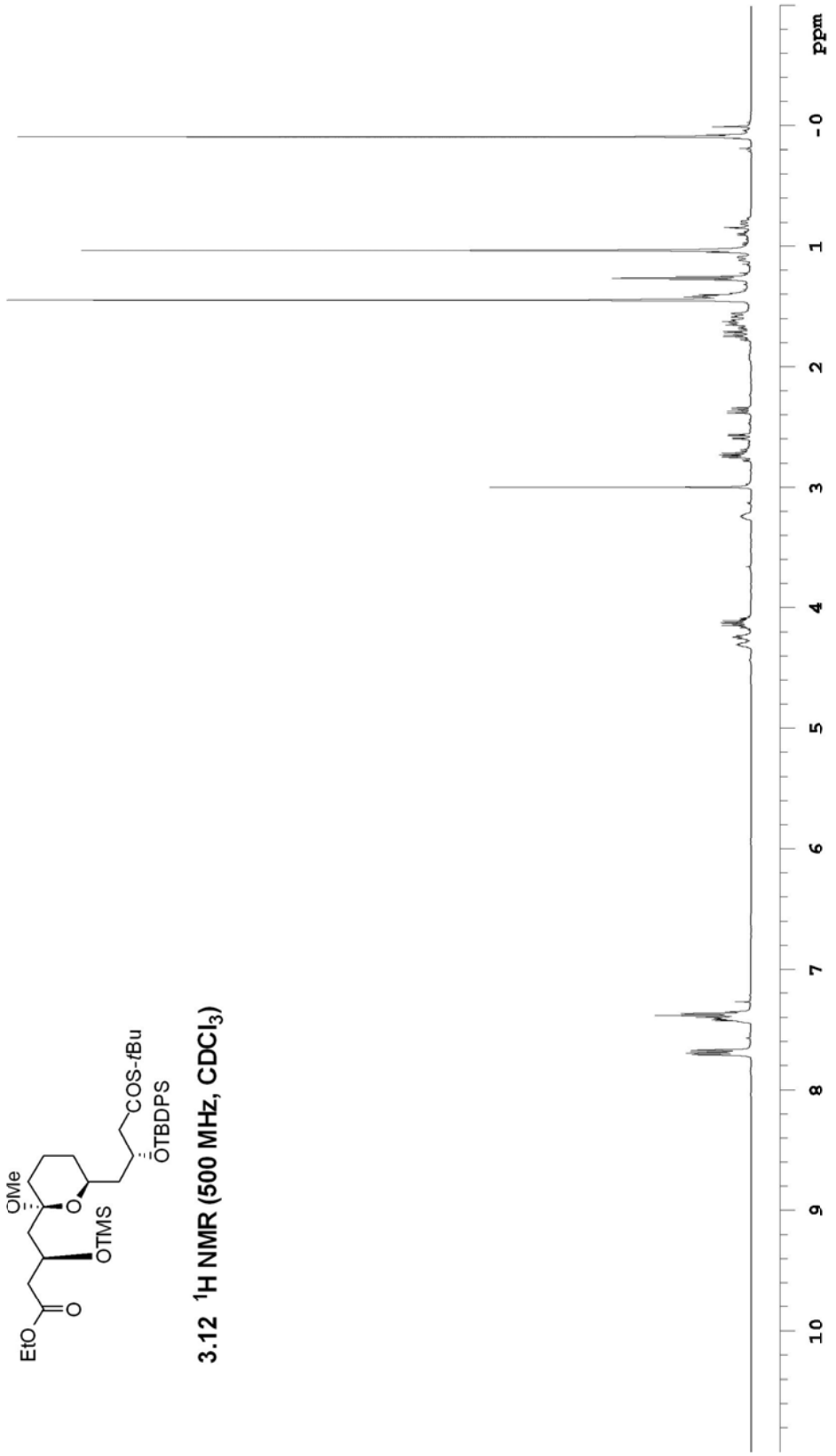


3.11 ^{1}H NMR (500 MHz, $CDCl_3$)

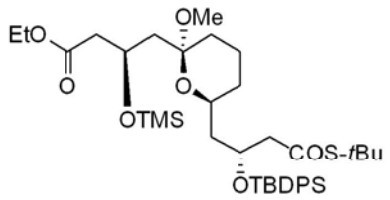


3.11 ^{13}C NMR (125 MHz, $CDCl_3$)

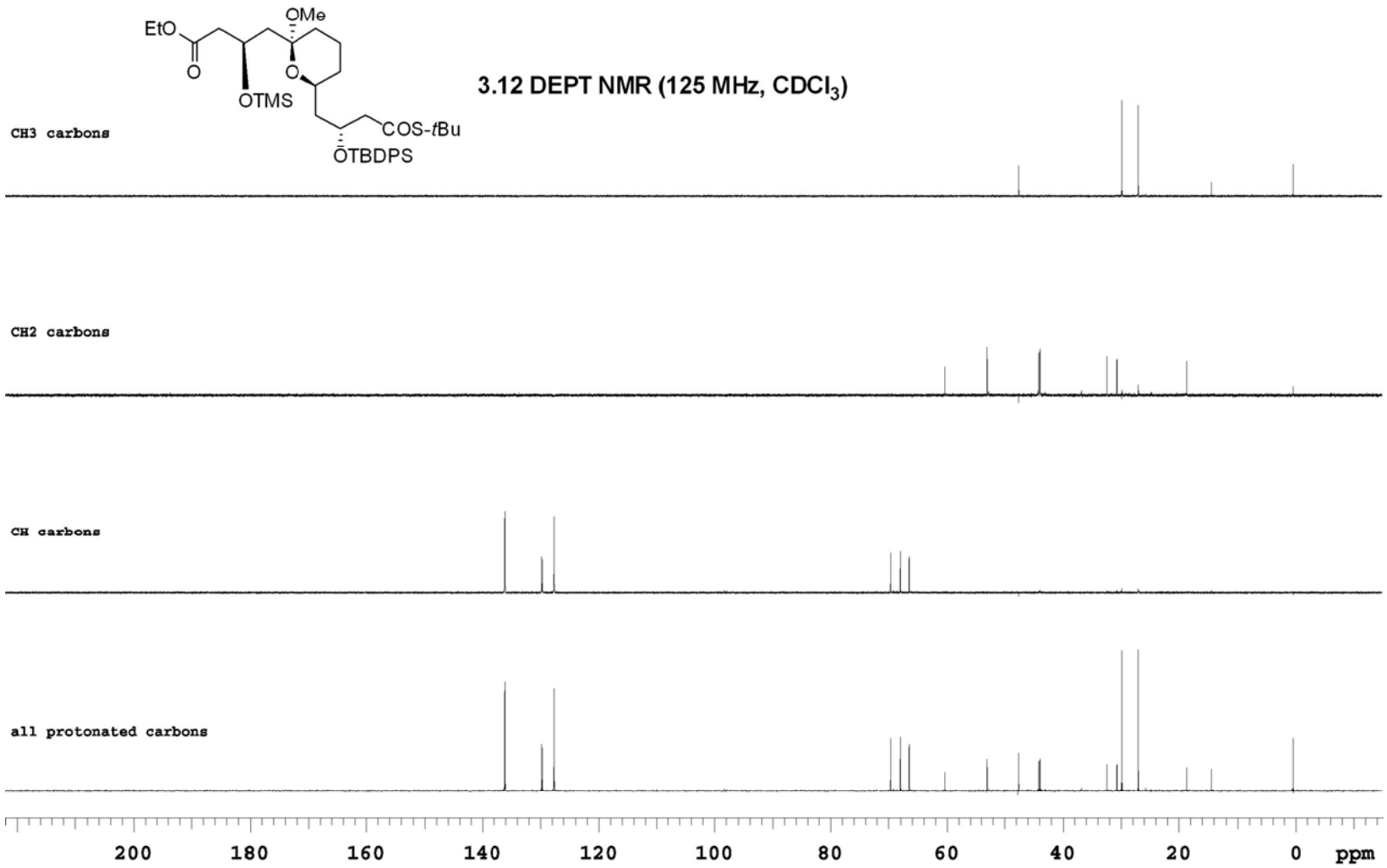

EtO
O
OTBS
O
OPMB
TBDPSO
O
S-tBu
3.11 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

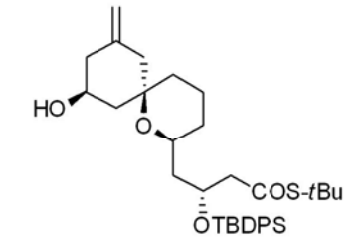


3.12 ^{1}H NMR (500 MHz, $CDCl_3$)

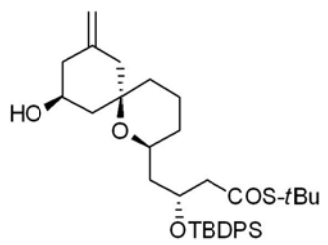


3.12 ^{13}C NMR (125 MHz, $CDCl_3$)

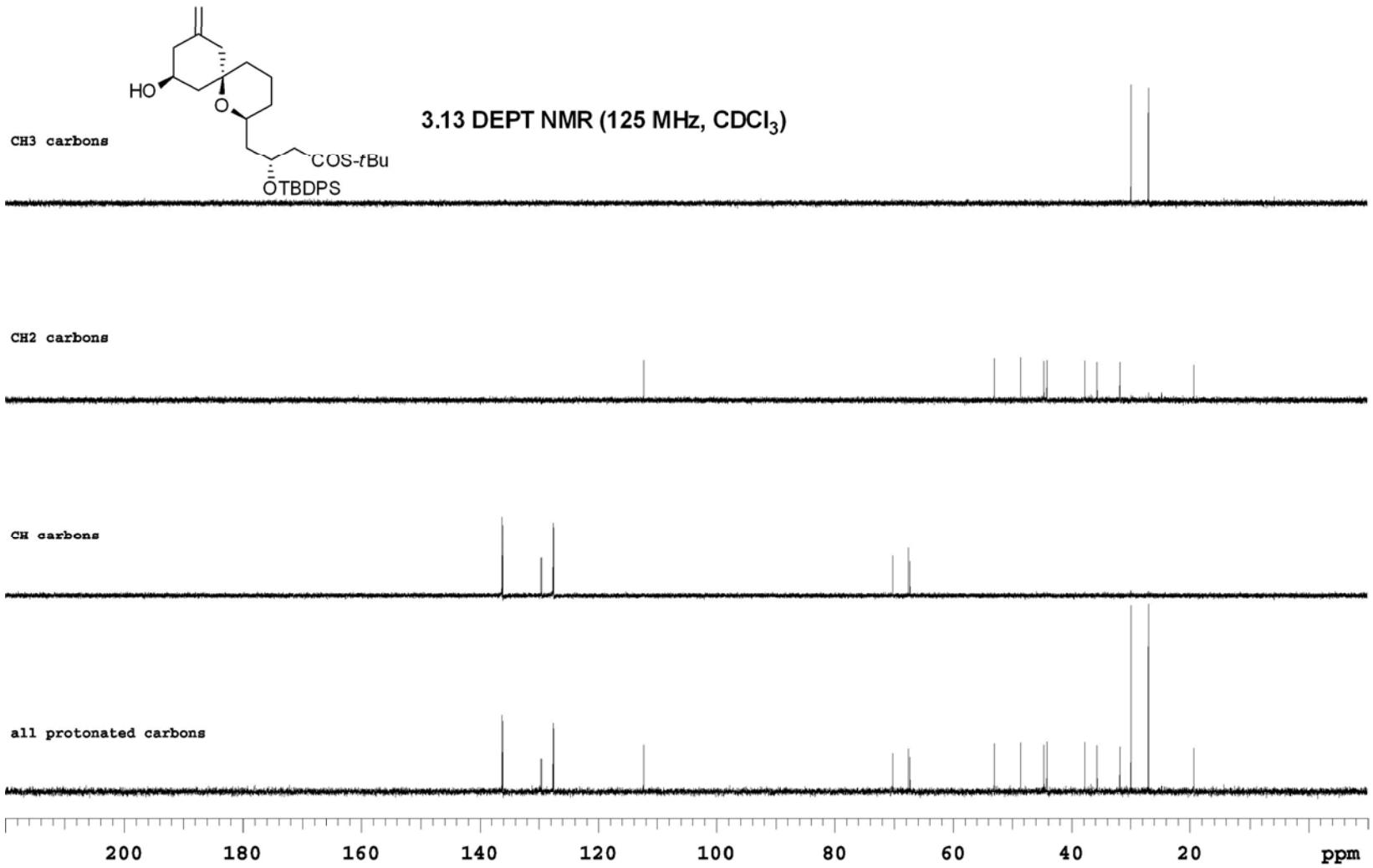

EtO
O
OMe
O
OTMS
COS-tBu
OTBDPS
3.12 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

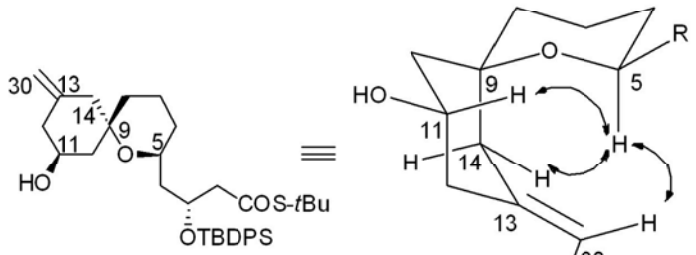


3.13 ^{1}H NMR (500 MHz, $CDCl_3$)

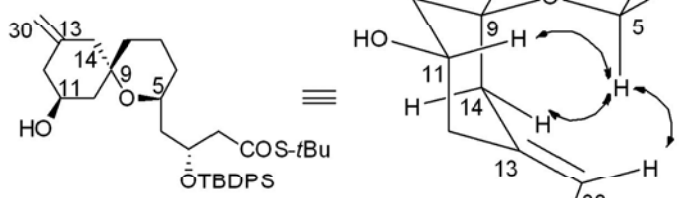


3.13 ^{13}C NMR (125 MHz, $CDCl_3$)

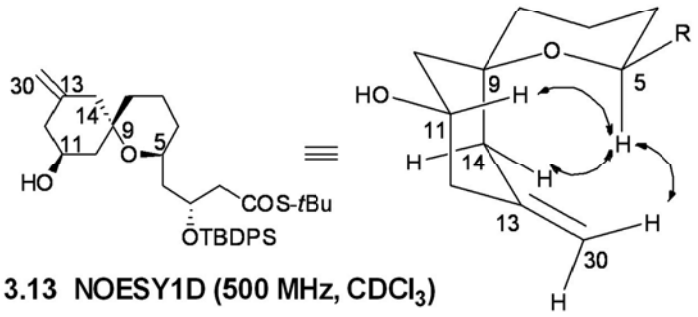

HO
O
COS-tBu
OTBDPS
3.13 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
ppm



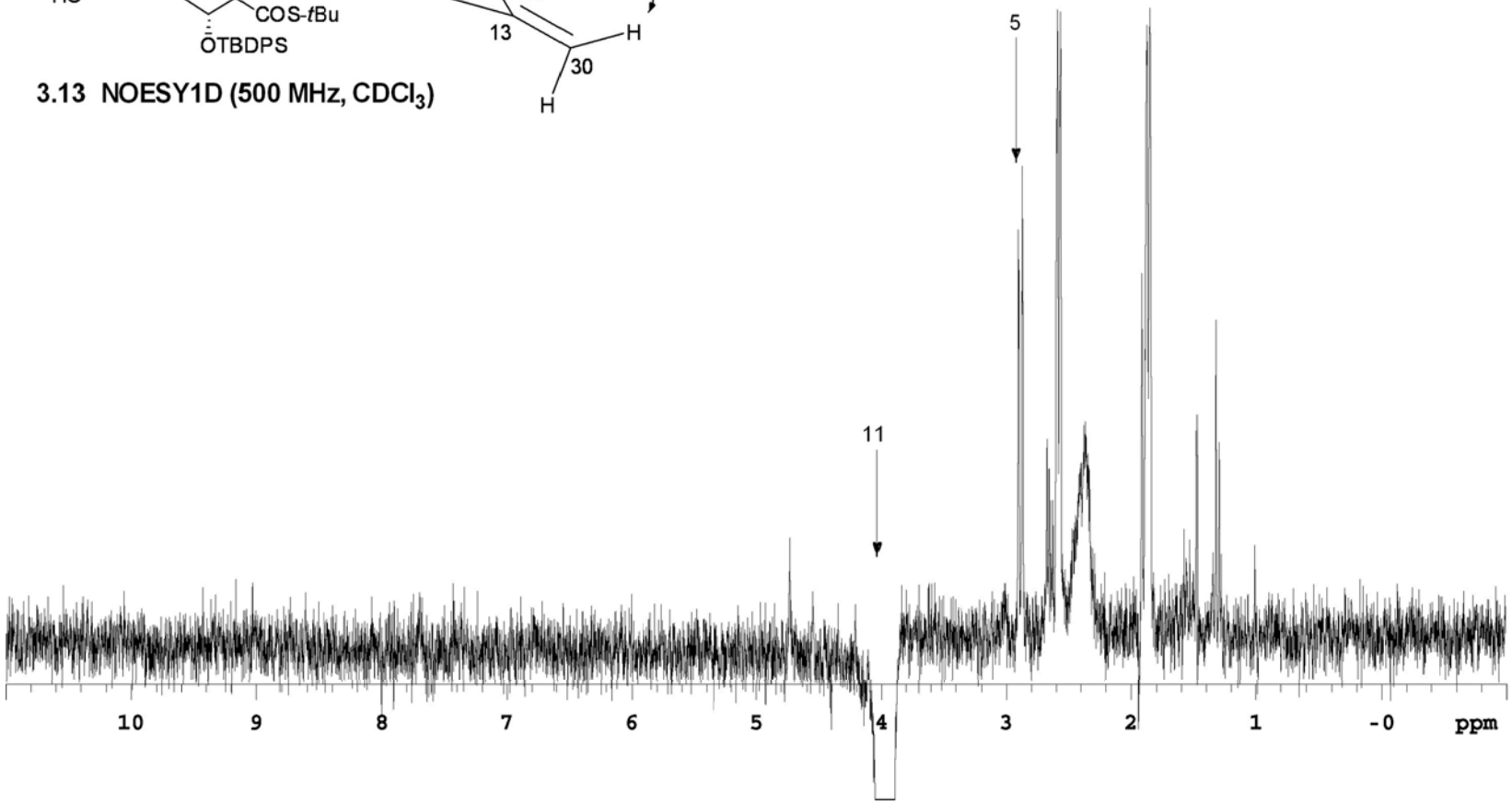
3.13 NOESY1D (500 MHz, $CDCl_3$)

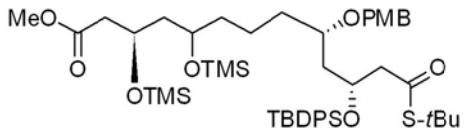


3.13 NOESY1D (500 MHz, $CDCl_3$)

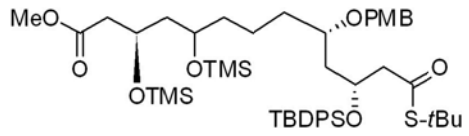


3.13 NOESY1D (500 MHz, $CDCl_3$)

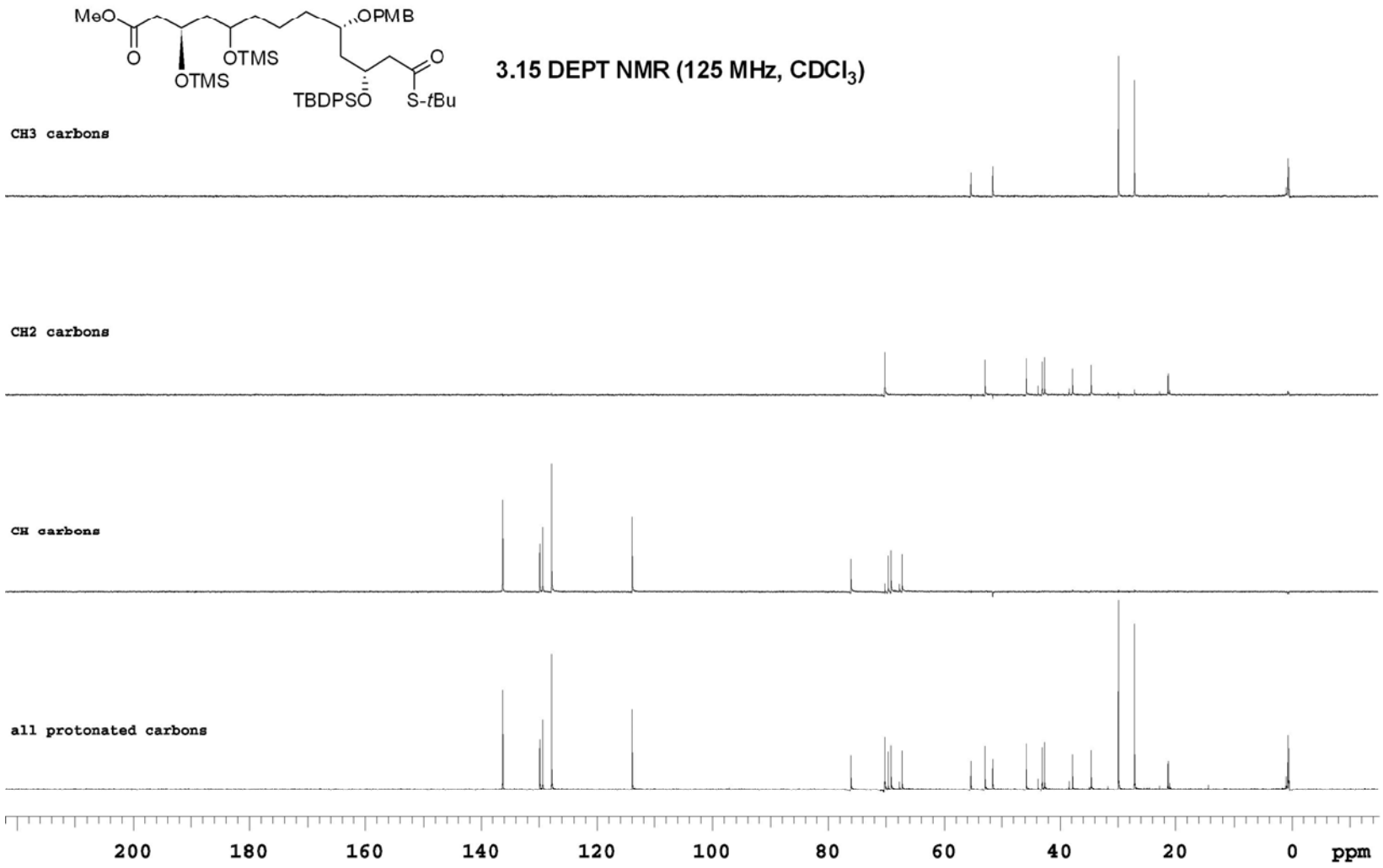


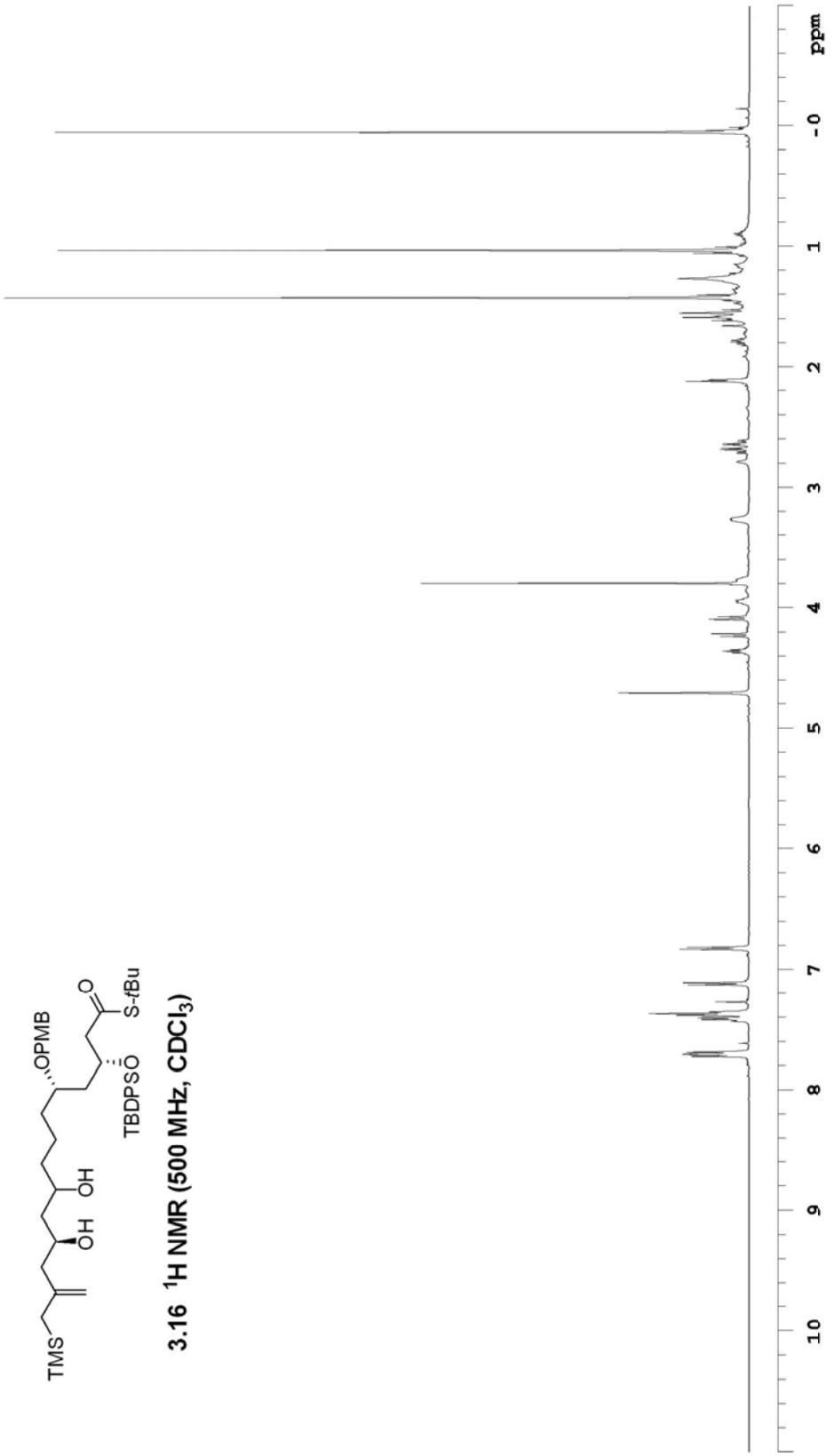


3.15 ^{1}H NMR (500 MHz, $CDCl_3$)

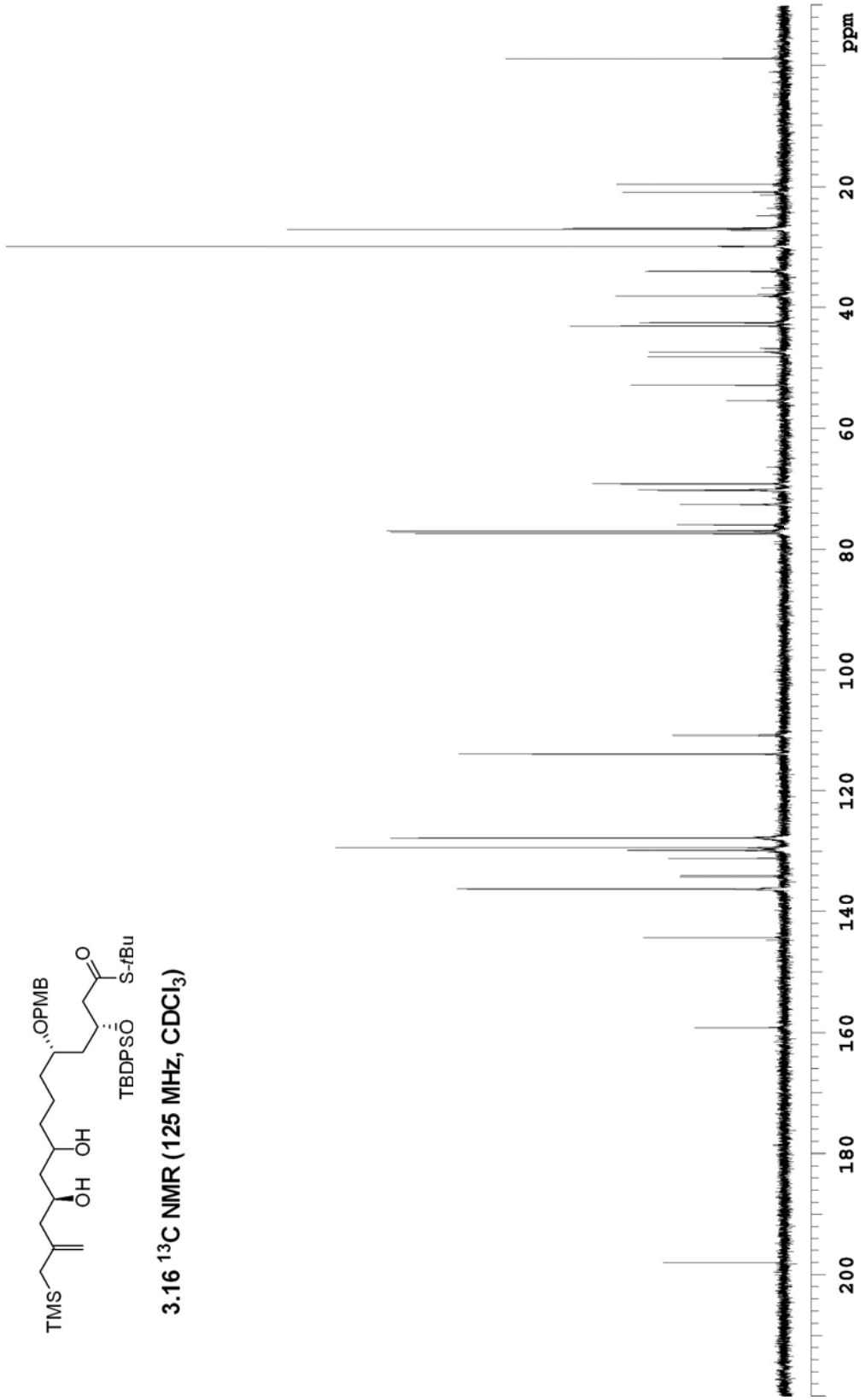


3.15 ^{13}C NMR (125 MHz, $CDCl_3$)

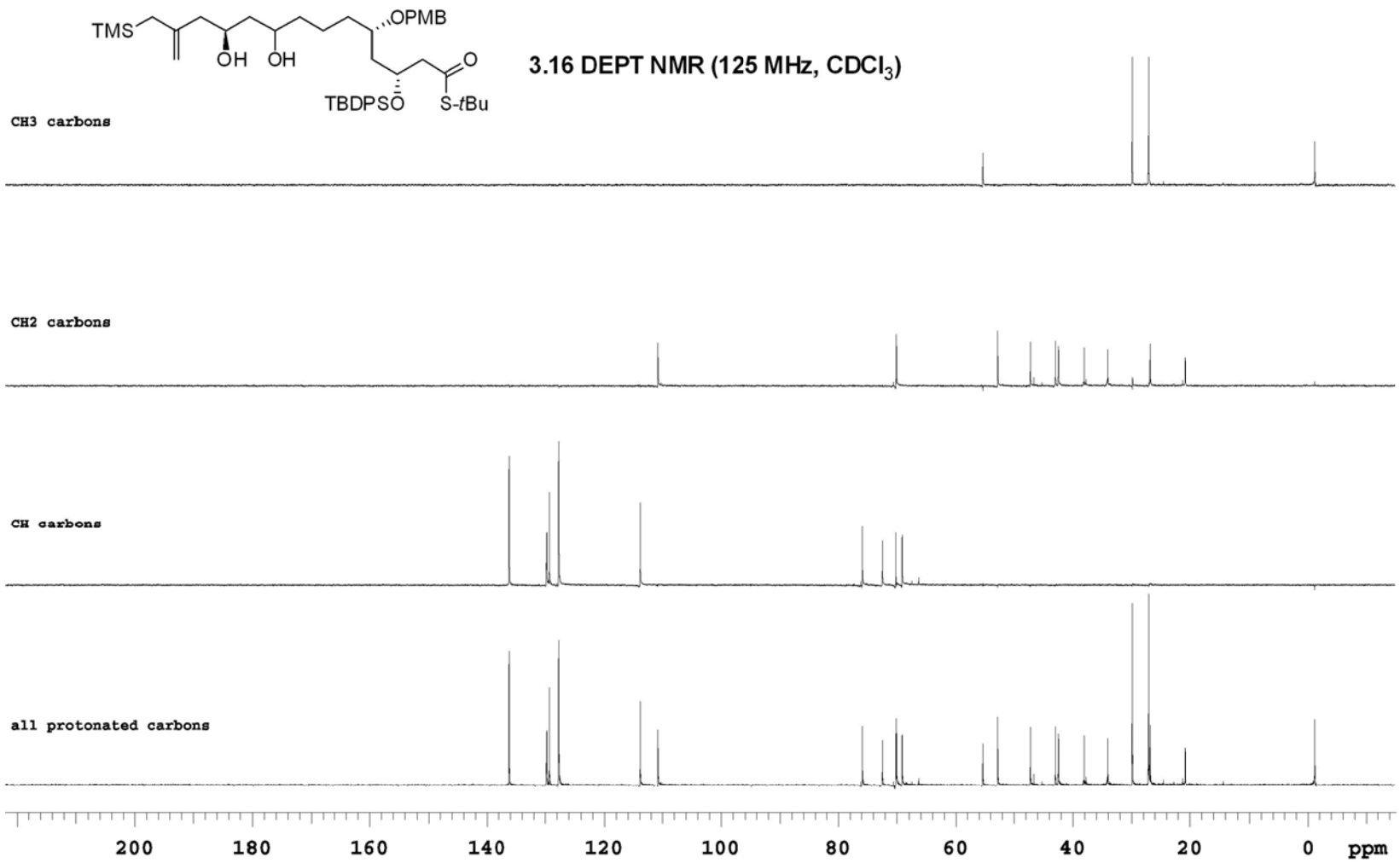

MeO
O
OTMS
OTMS
OPMB
TBDPSO
O
S-tBu
3.15 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

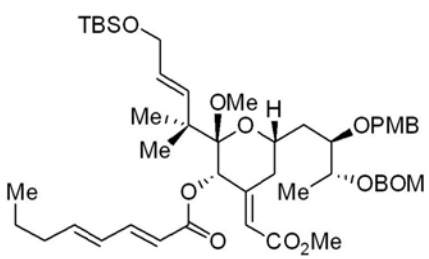


3.16 ^{1}H NMR (500 MHz, $CDCl_3$)

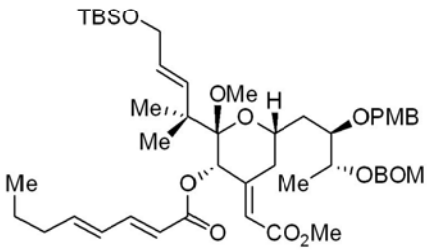


3.16 ^{13}C NMR (125 MHz, $CDCl_3$)

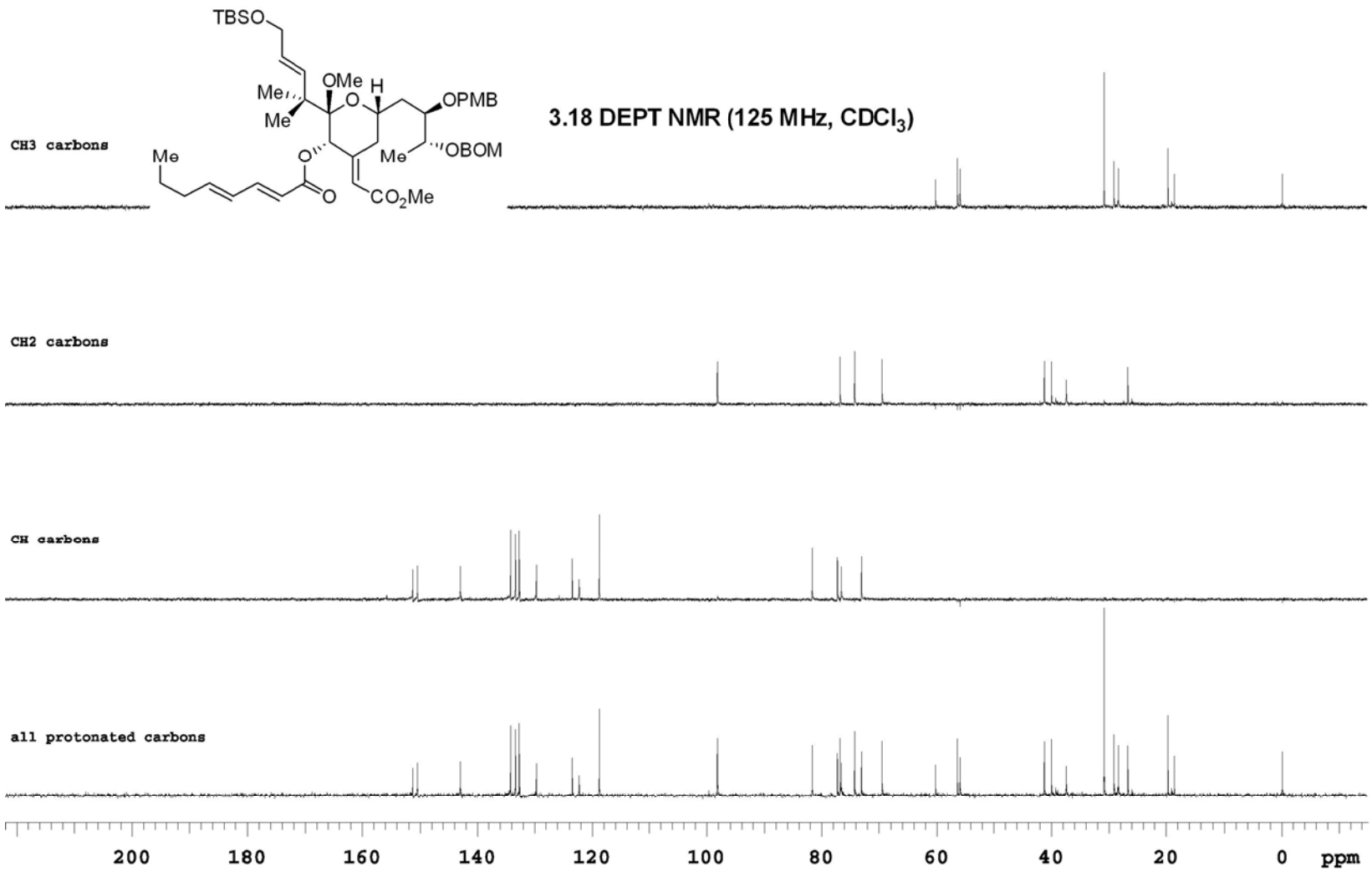

TMS
OH
OH
OPMB
TBDPSO
O
S-tBu
3.16 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

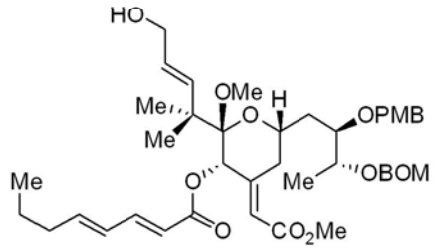


3.18 ^{1}H NMR (500 MHz, $CDCl_3$)

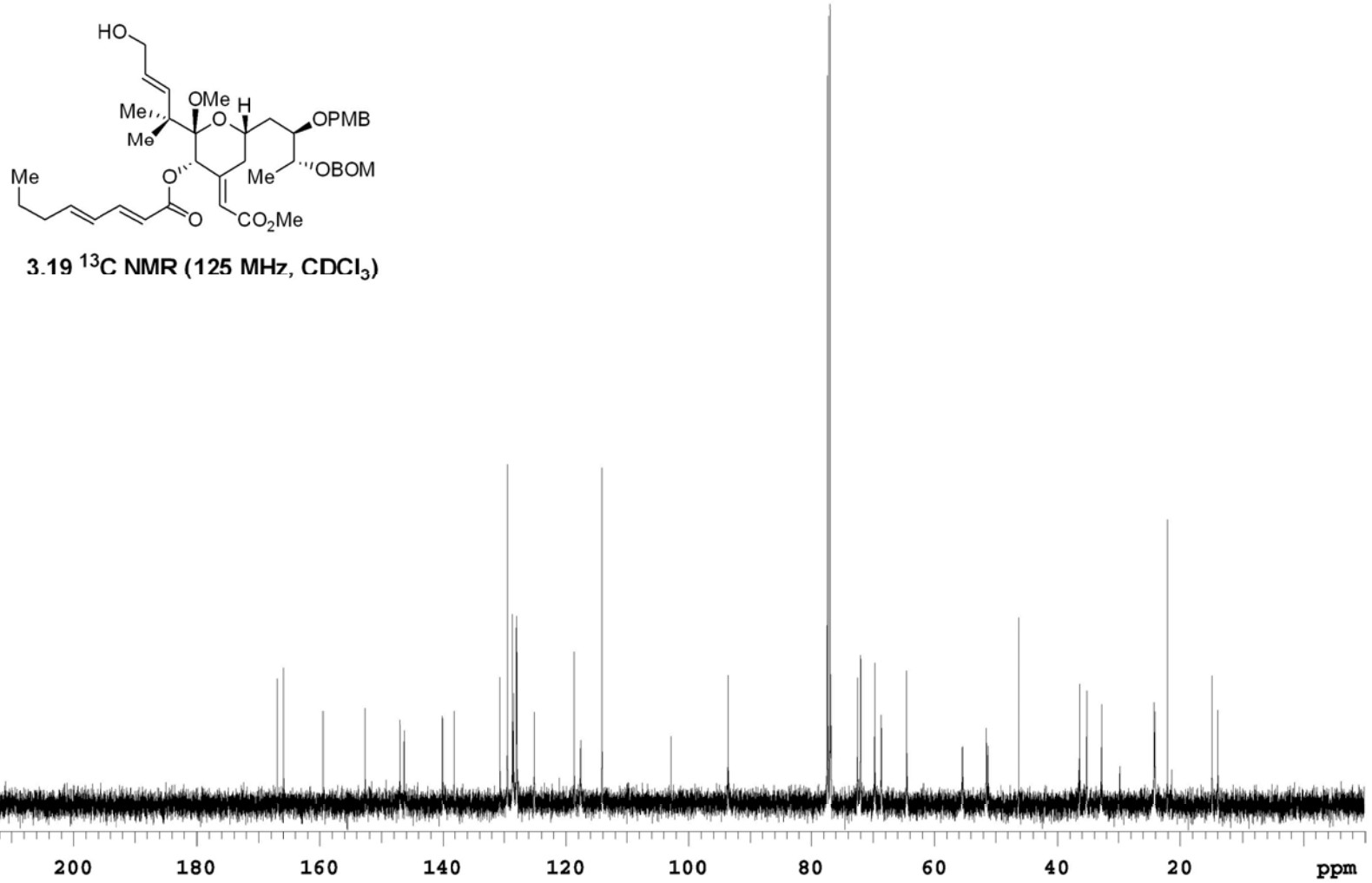


3.18 ^{13}C NMR (125 MHz, $CDCl_3$)

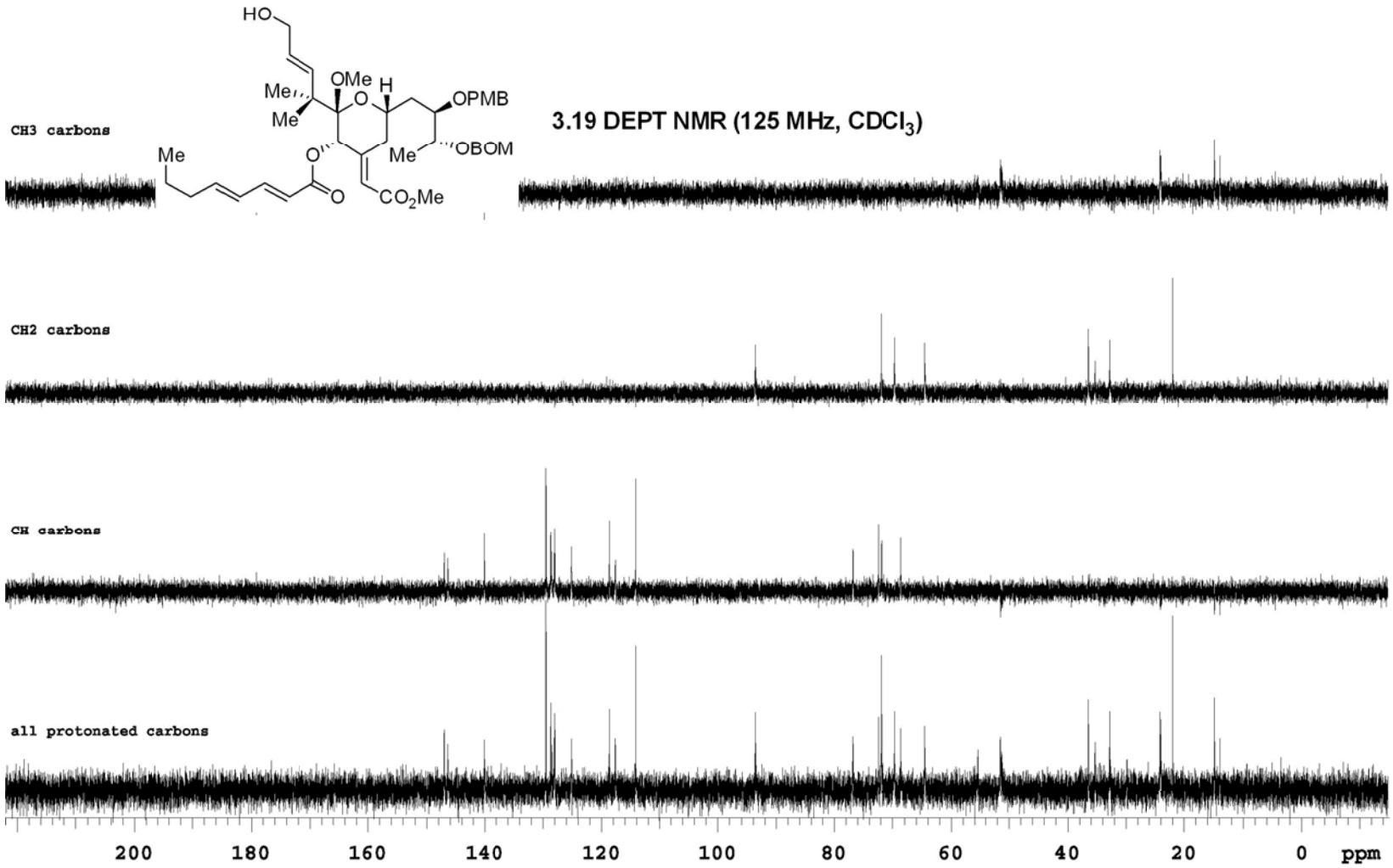

TBSO
OMe
H
Me
Me
O
OPMB
Me
Me
OBOM
O
O
O
CO2Me
3.18 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

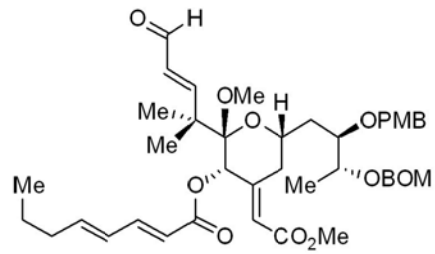


3.19 ^{1}H NMR (500 MHz, $CDCl_3$)

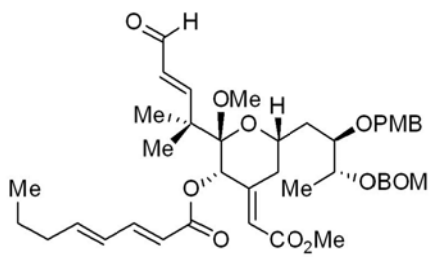


3.19 ^{13}C NMR (125 MHz, $CDCl_3$)

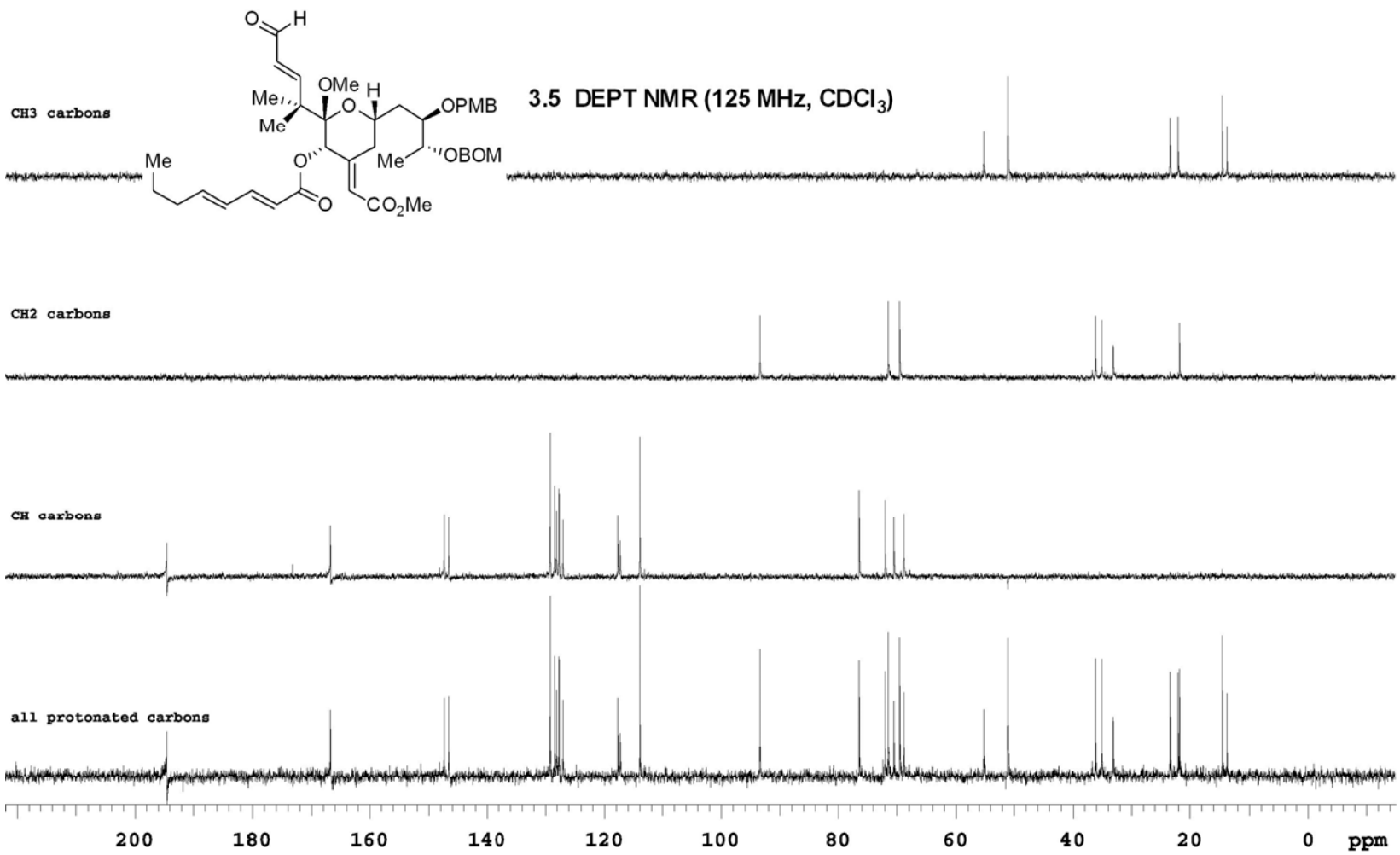

HO
OMe
H
Me
Me
O
OPMB
Me
Me
OBOM
O
O
CO2Me
3.19 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

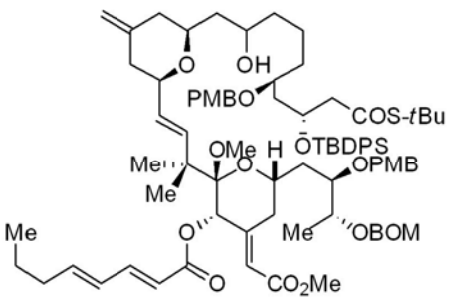


3.5 ^{1}H NMR (500 MHz, $CDCl_3$)

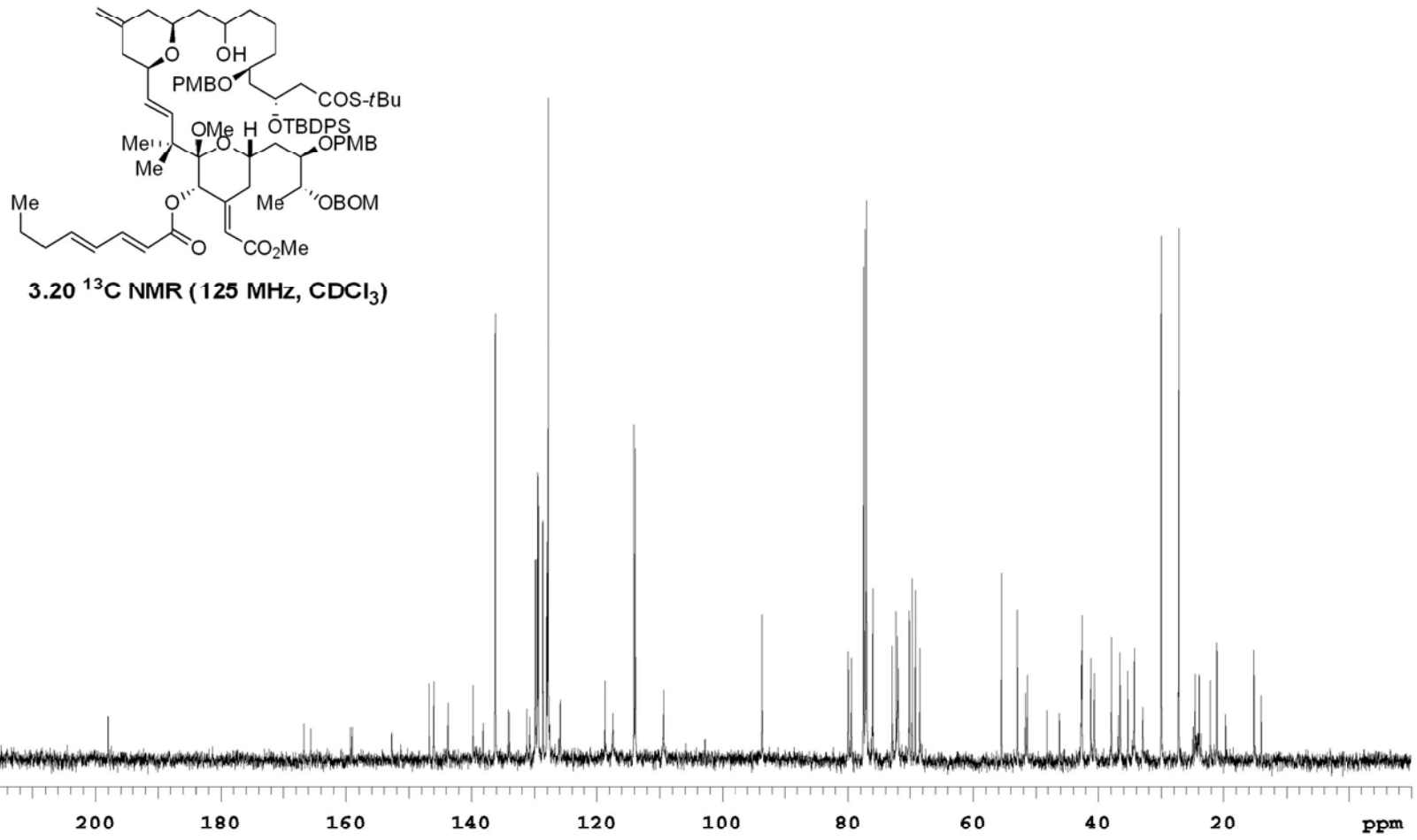


3.5 ^{13}C NMR (125 MHz, $CDCl_3$)

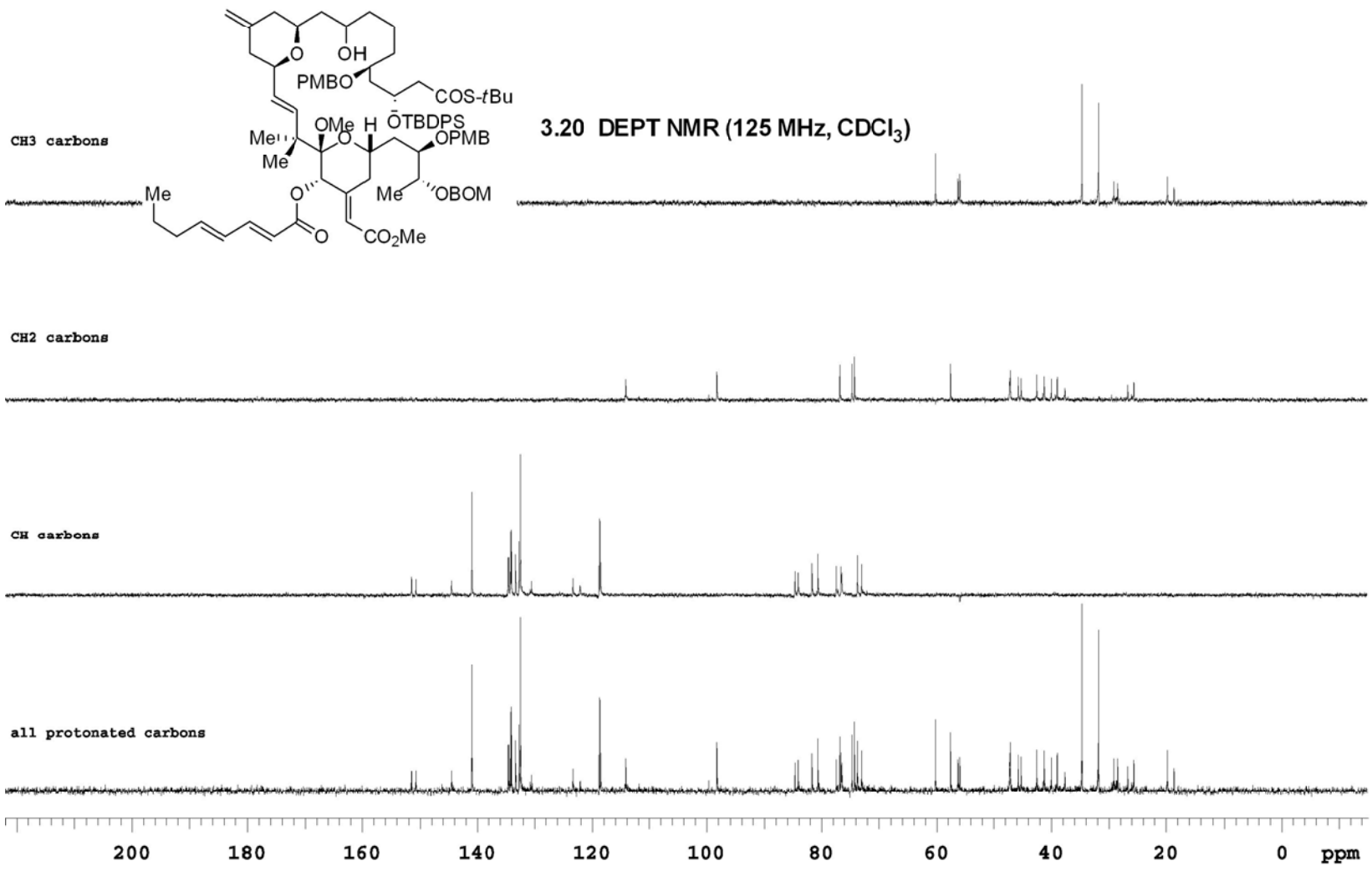

3.5 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OMe
H
OPMB
OBOM
Me
CO2Me
200
180
160
140
120
100
80
60
40
20
0
ppm

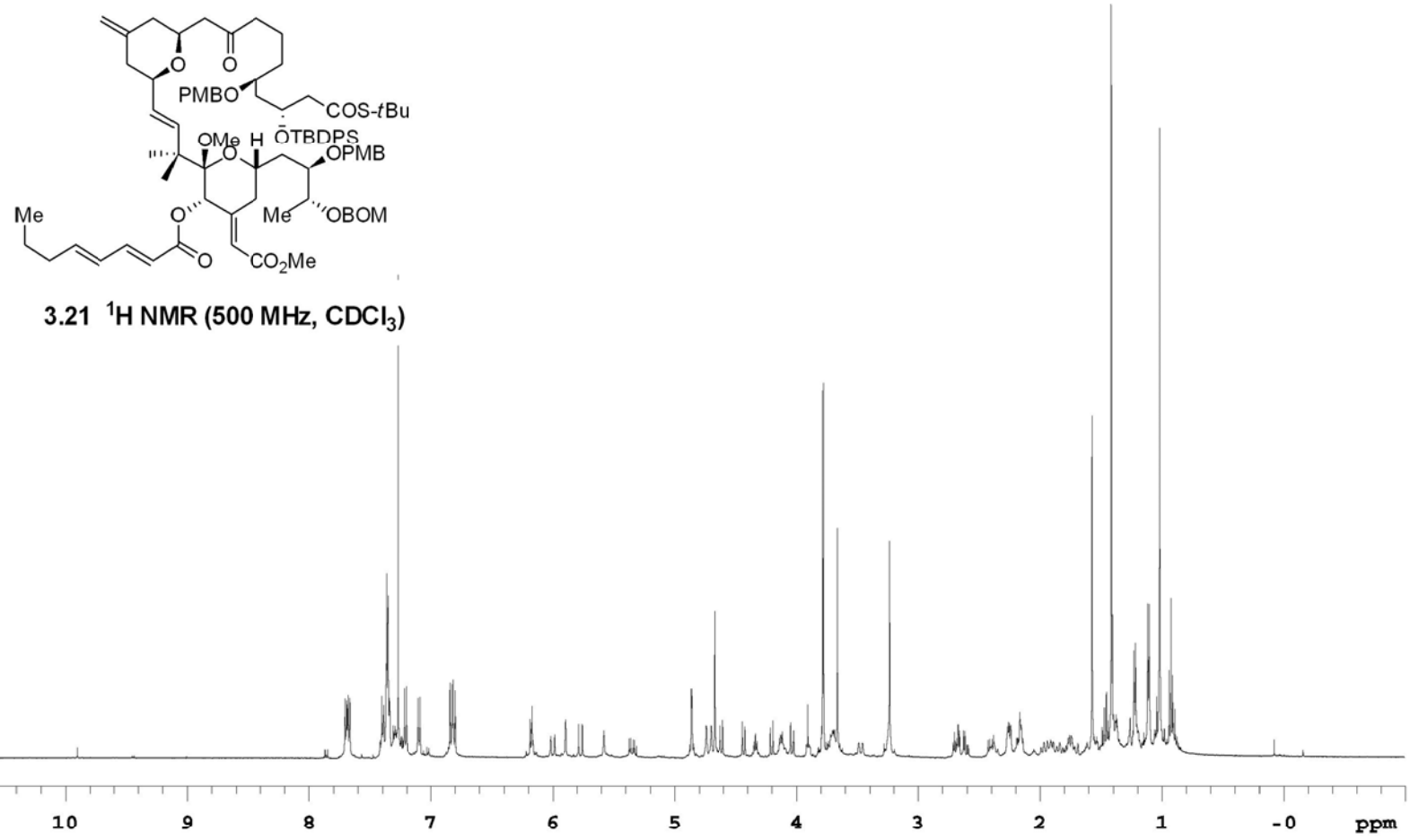


3.20 ^{1}H NMR (500 MHz, $CDCl_3$)

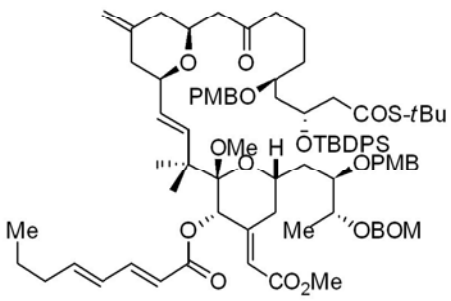


3.20 ^{13}C NMR (125 MHz, $CDCl_3$)

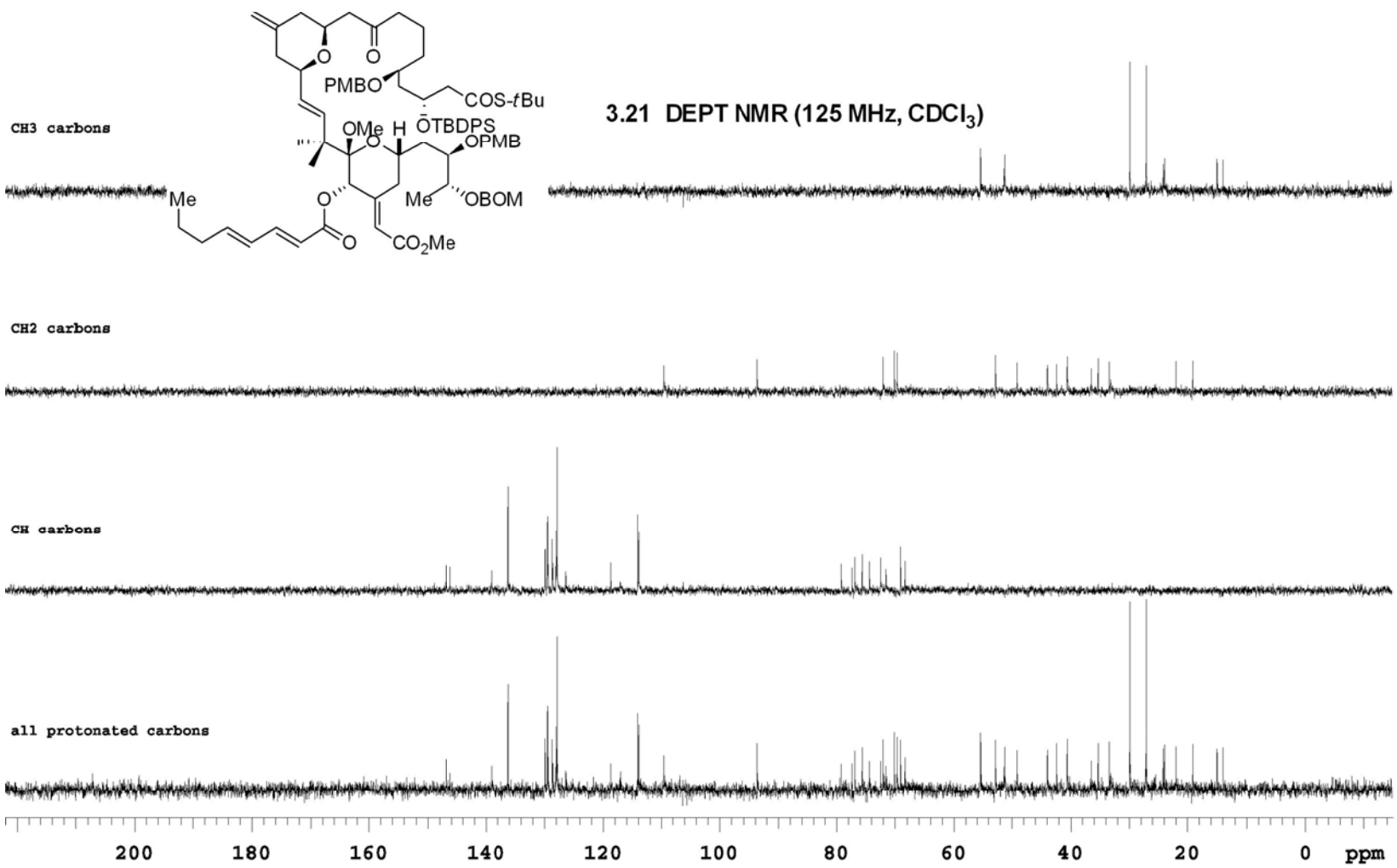

3.20 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
PMBO
OH
COS-tBu
OTBDPS
OMe
H
OPMB
Me
Me
Me
OBOM
CO2Me
200
180
160
140
120
100
80
60
40
20
0
ppm

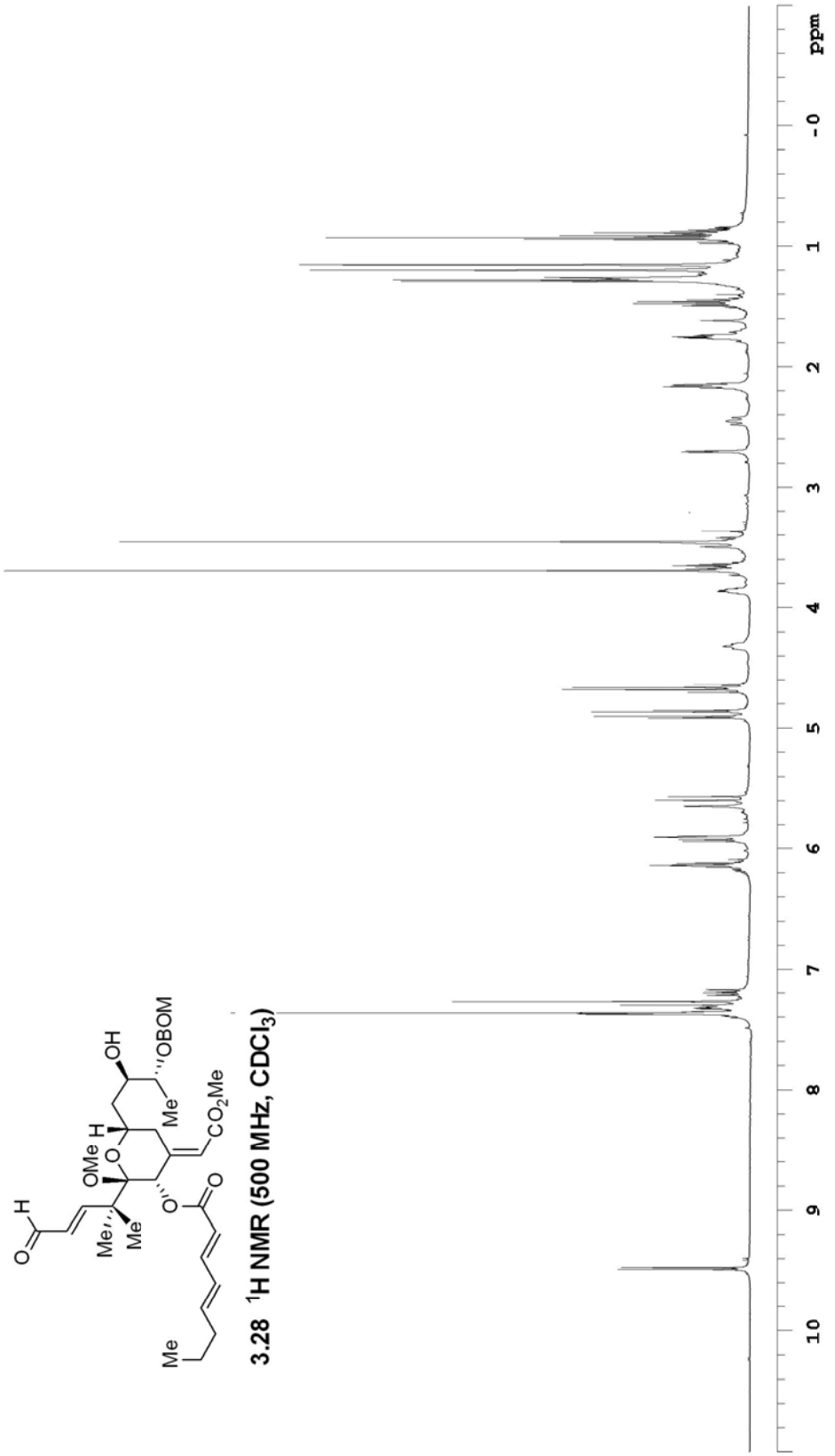


3.21 ^{1}H NMR (500 MHz, $CDCl_3$)

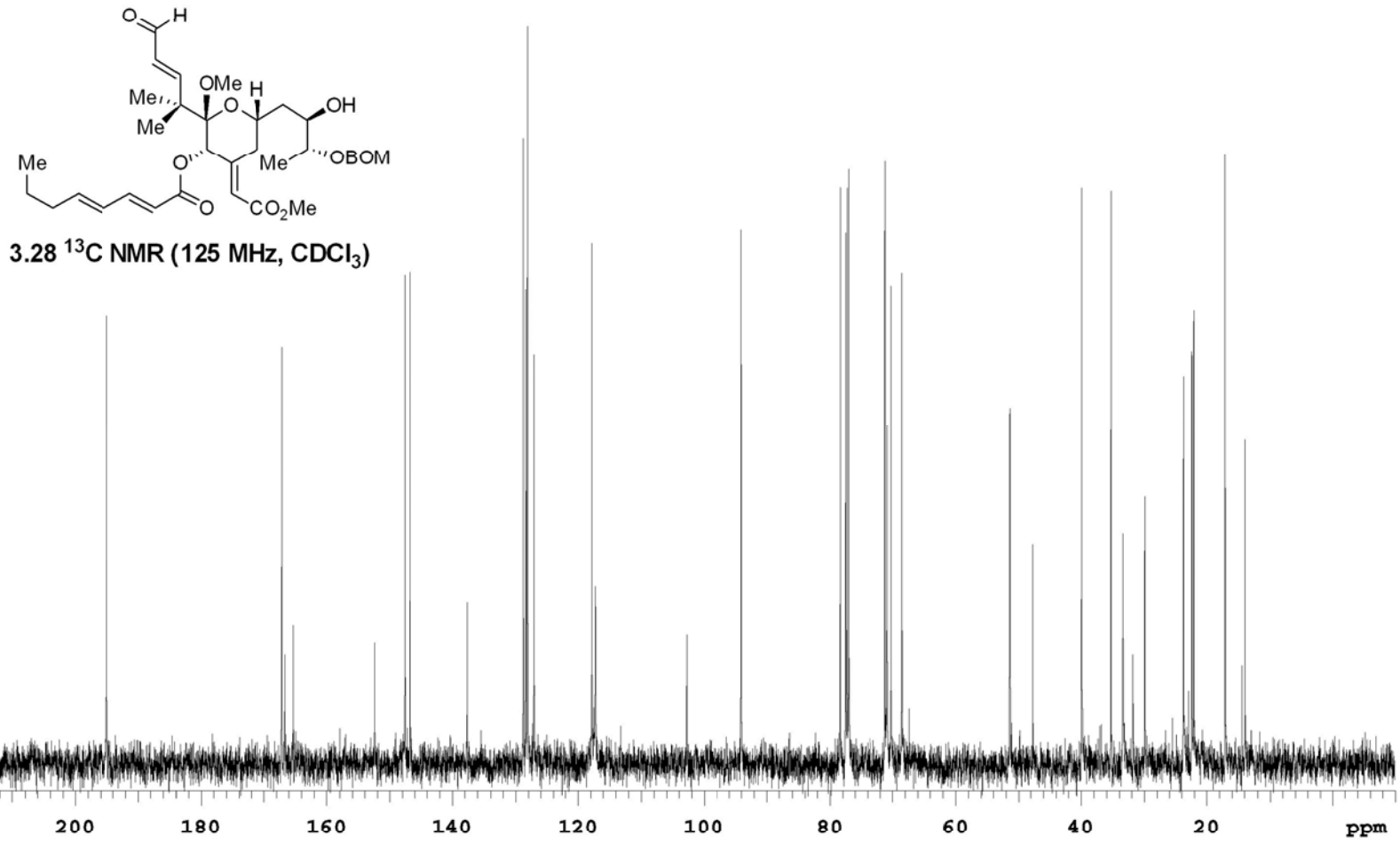


3.21 ^{13}C NMR (125 MHz, $CDCl_3$)

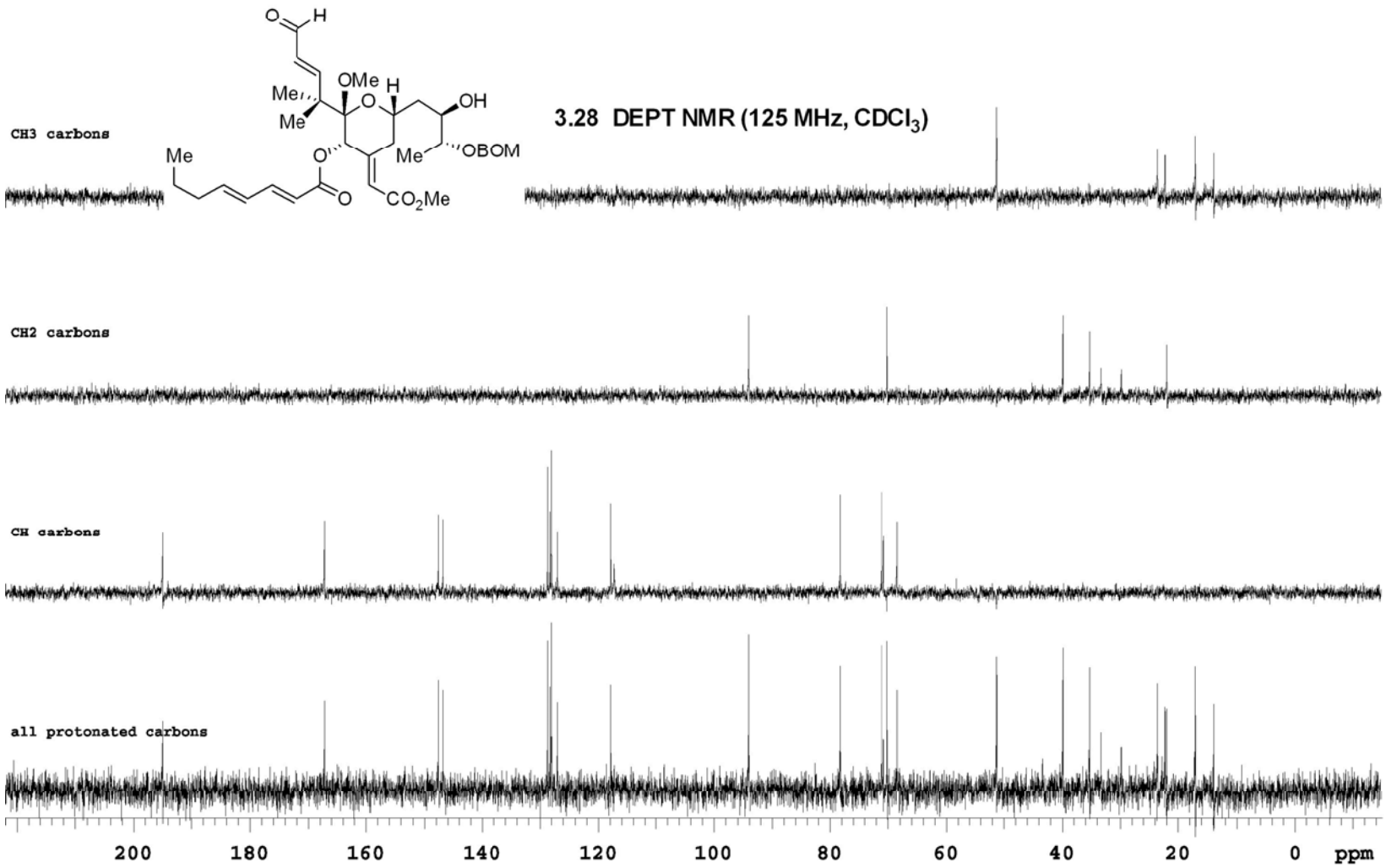

3.21 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
PMBO
COS-tBu
OMe
H
OTBDPS
OPMB
Me
OBOM
Me
CO2Me
200
180
160
140
120
100
80
60
40
20
0
ppm

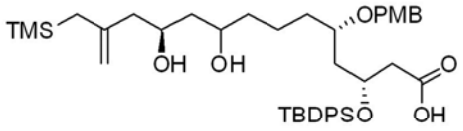


3.28 ^{1}H NMR (500 MHz, $CDCl_3$)

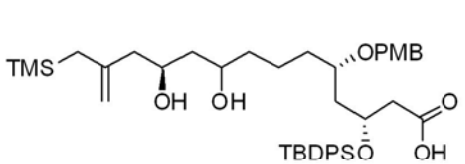


3.28 ^{13}C NMR (125 MHz, $CDCl_3$)

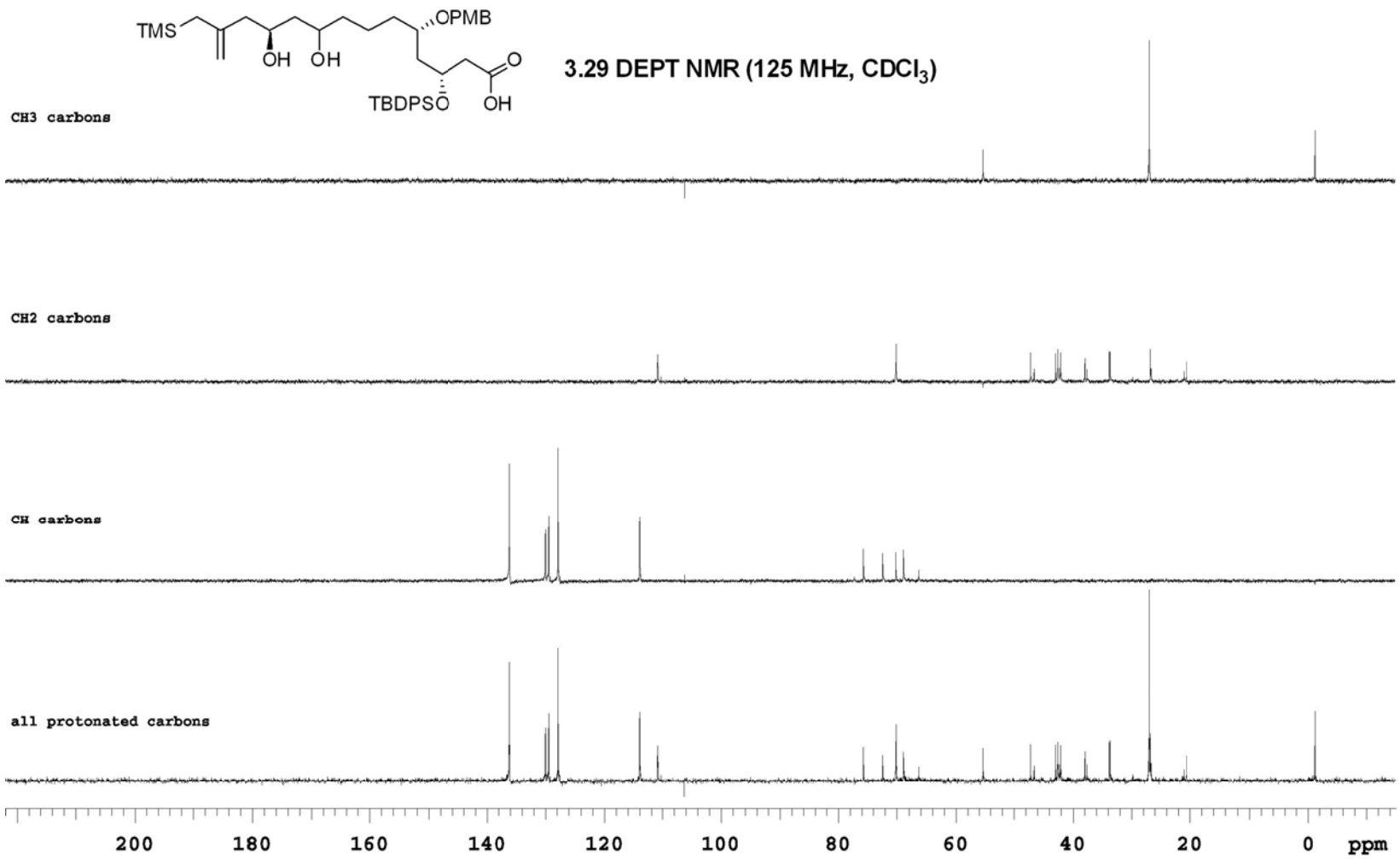

3.28 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
OMe
H
OH
Me
Me
Me
OBOM
CO2Me
200
180
160
140
120
100
80
60
40
20
0
ppm

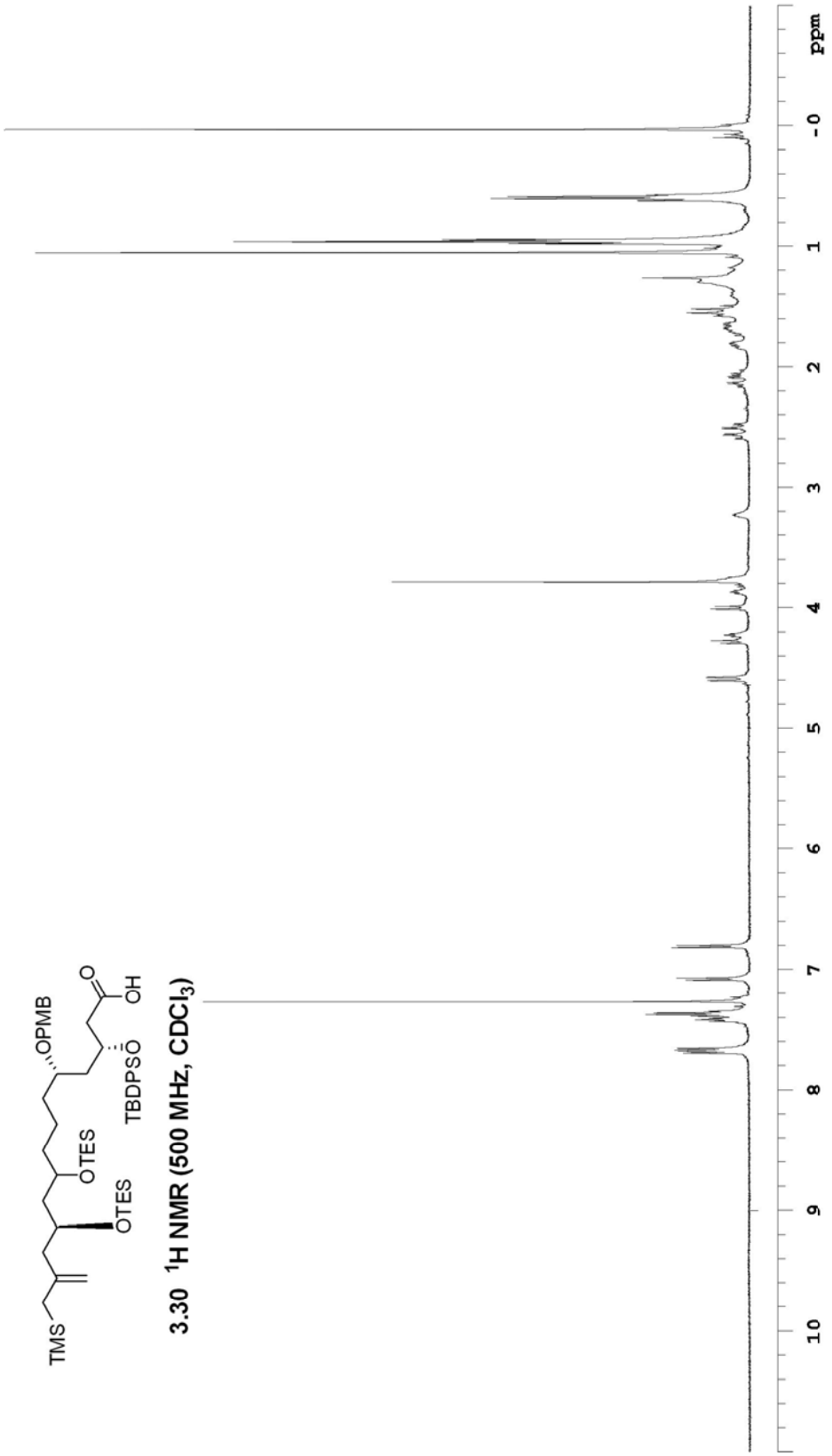


3.29 ^{1}H NMR (500 MHz, $CDCl_3$)

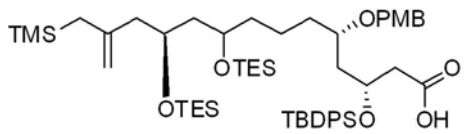


3.29 ^{13}C NMR (125 MHz, $CDCl_3$)

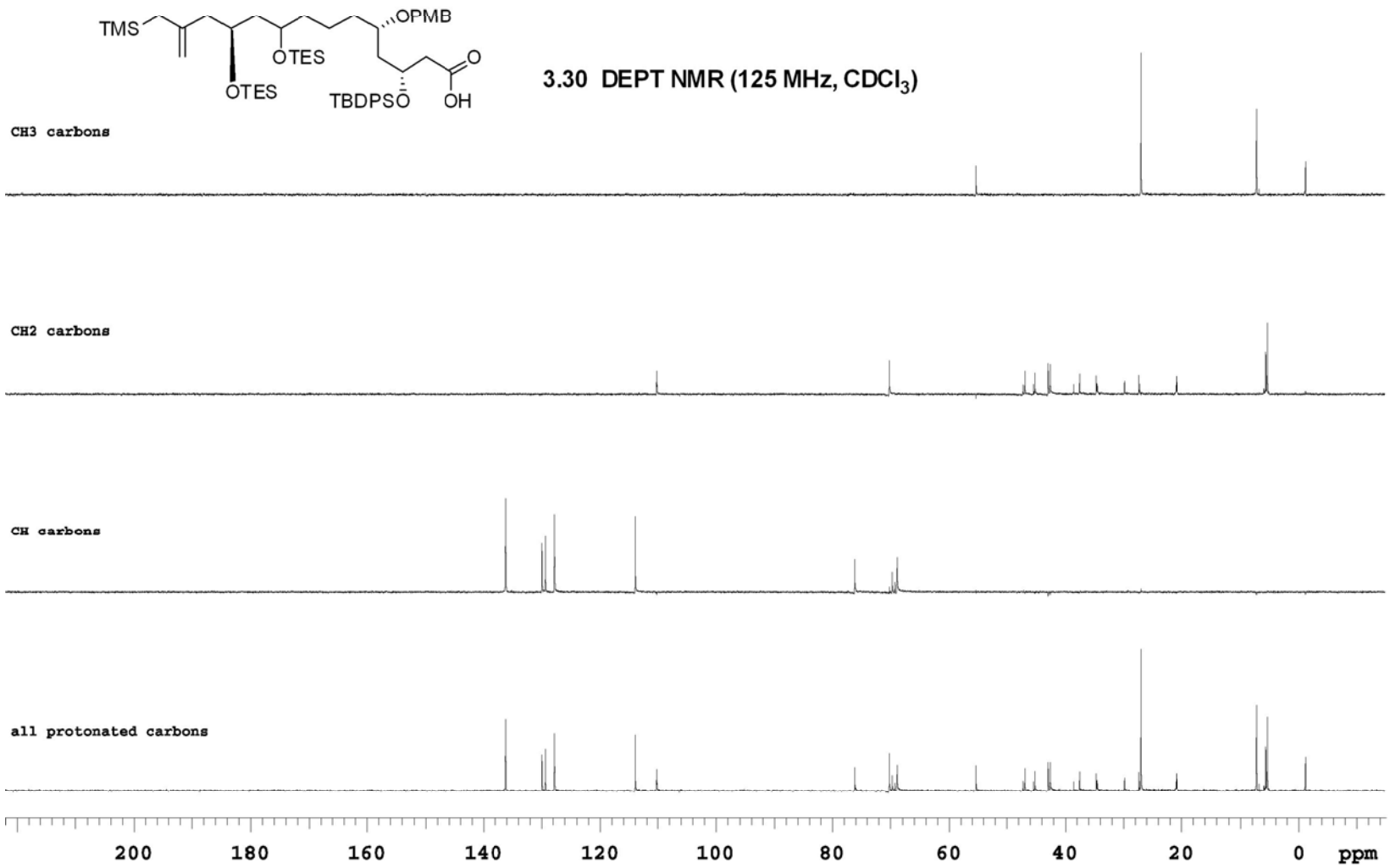

TMS
OH
OH
OPMB
TBDPSO
O
OH
3.29 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm

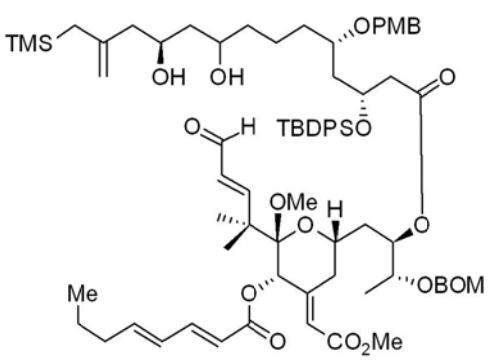


3.30 ^{1}H NMR (500 MHz, $CDCl_3$)

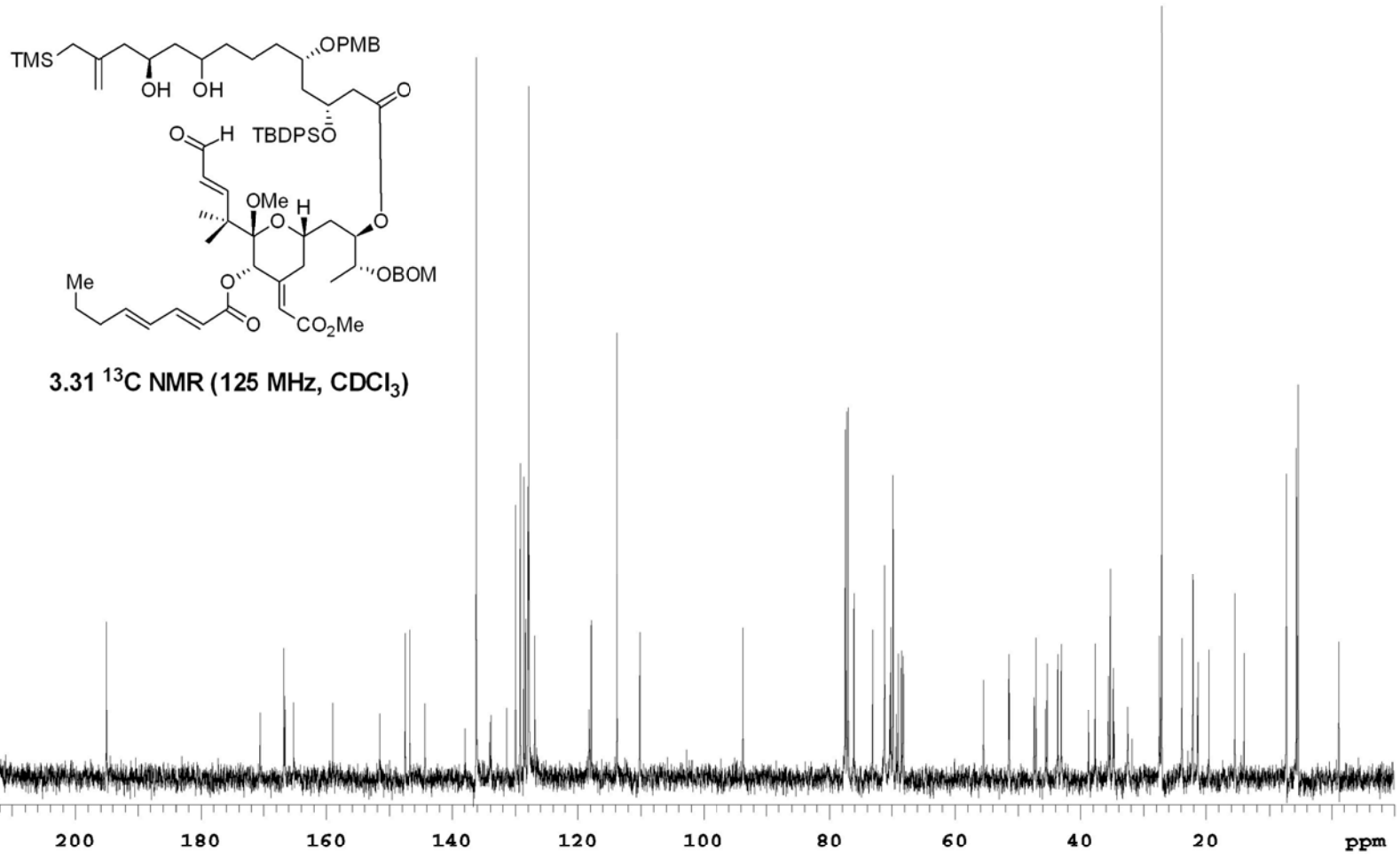


3.30 ^{13}C NMR (125 MHz, $CDCl_3$)

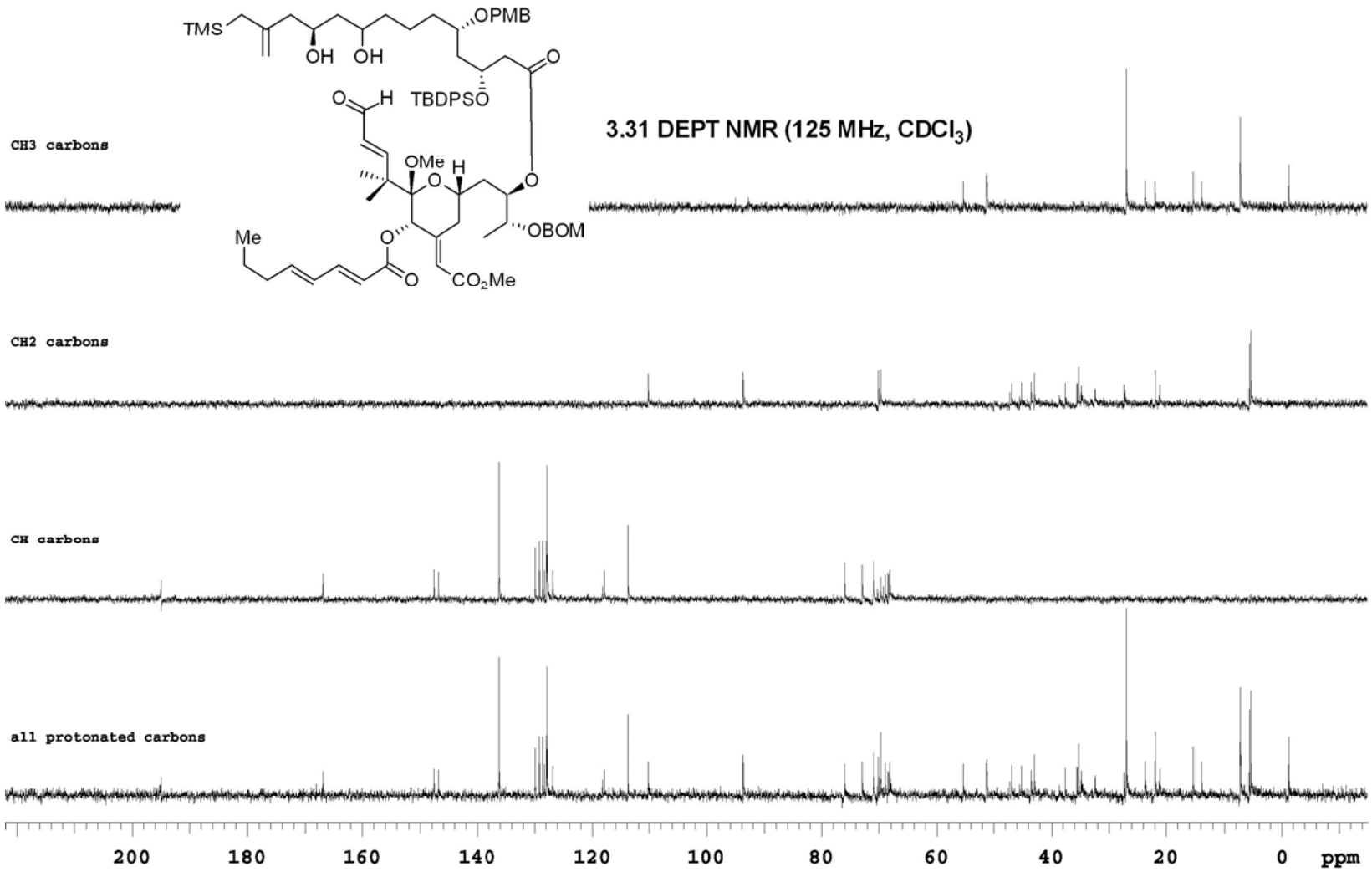

TMS
OTES
OTES
TBDPSO
OPMB
O
OH
3.30 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm



3.31 ^{1}H NMR (500 MHz, $CDCl_3$)



3.31 ^{13}C NMR (125 MHz, $CDCl_3$)


TMS
OH
OH
OPMB
O
H
TBDPSO
OMe
H
O
O
OBOM
Me
O
O
CO2Me
3.31 DEPT NMR (125 MHz, CDCl3)
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm